

# THE ENDOCRINOLOGIST

THE MAGAZINE OF THE SOCIETY FOR ENDOCRINOLOGY

Insights  
into

## ADRENAL ENDOCRINOLOGY

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# A word from THE EDITOR...



Well, here it is. Two years have passed, predominantly during a pandemic, and this is my last editorial for *The Endocrinologist*. Looking back, I can't put into words what I, and I'm sure all of you reading this, have experienced: parenting, work, having COVID, being repurposed as needed, realising life will never be the same. At least I was spared home schooling. But, within all this, there was learning to have joy and to be grateful.

During peak COVID times, we decided not to commission an entire new issue but, instead, rummaged through the archives. I hope remembering times gone by made you smile.

The Society has been amazingly supportive throughout the last two years. Stephanie Baldeweg, Chair of the Clinical Committee, galvanised us so we could set up resources to keep our patients safe in the early part of the pandemic. We set up the adrenal crisis web page ([www.endocrinology.org/adrenal-crisis](http://www.endocrinology.org/adrenal-crisis)) to share information. Now we have the output of the Future of Endocrinology working group to support the reimagining of service delivery, as we rebuild and recover. I hope we carry on working in this collaborative way, sharing information, ideas, talks and resources.

Huge thanks are due to *The Endocrinologist* crew, Kim Jonas, Doug Gibson, Louise Hunter and Craig Doig, for fun meetings where we thrashed around ideas, titles and terrible jokes. I also thank Jane Shepley, our Managing Editor, who corrals content into a magazine and Lynsey Forsyth in the Society HQ, for pulling together Society content. We have worked very happily virtually for the last 2 years, saving time, money and the planet. Plans now are to create an online version of *The Endocrinologist*, to further improve our green credentials.

I am terrible at endings. I'd like to say that the crew and I said our fond farewells in Edinburgh, but Kim and I were too busy dancing in our jumpsuits of joy (Doug, Craig – your dance floor absences were noted). So, here are The Beatles saying goodbye, as only they could – probably the best ever final live concert, or more aptly, a piece of history: <https://bit.ly/3lkDDWL>.

I'm sure I'll see you all soon, on Twitter or in Harrogate, if not before. Keep sending through amazing content. I'm sure *The Endocrinologist* will go from strength to strength with Kim as Editor.

HELEN SIMPSON

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**Become a contributor...** Contact the Editorial office at [endocrinologist@endocrinology.org](mailto:endocrinologist@endocrinology.org)

The Society welcomes news items, contributions, article suggestions and letters to the Editor. We would also like to hear your feedback on this issue of the magazine.

Deadline for news items for the SPRING 2022 issue: **12 January 2022.**

Front cover image ©Shutterstock

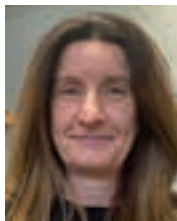


# Happy holidays to all our readers



## WITH THANKS

In November, Eleanor Davies and Duncan Bassett finished their terms of office as Society General Secretary and Programme Secretary respectively. Our grateful thanks go to both of them for all their hard work and input during their tenure. Turn to page 26 to learn more about their successors and their plans.



Eleanor Davies



Duncan Bassett

## COULD SOCIETY MEMBERS HELP YOU?

Does your research need input from the wider endocrine community?

Send us your audits, surveys and research projects and we will promote them to members.

Go to [www.endocrinology.org/sharemywork](http://www.endocrinology.org/sharemywork) to submit yours and to take part in current projects.

## NEW GIRFT REPORT ON ENDOCRINOLOGY

The Getting It Right First Time (GIRFT) national report for endocrinology, by John Wass and Mark Lansdown, adds to the growing evidence that consolidating thyroid, parathyroid, adrenal and pituitary surgery can lower the rate of complications, improve surgery outcomes and reduce the length of hospital stays. Log in to [www.future.nhs.uk](http://www.future.nhs.uk) to read the full report with recommendations.



Márta Korbonits

## PRESIDENT-ELECT ANNOUNCED!

Márta Korbonits is Professor of Endocrinology and Metabolism, Centre Lead for Endocrinology and Deputy Institute Director at William Harvey Research Institute at Barts and the London School of Medicine and Dentistry, Queen Mary University of London. She has been an enthusiastic and valuable member of the Society for many years and we look forward to welcoming her as President at the 2022 AGM.

## EARLY CAREER GRANT FUNDING AVAILABLE

The Bioscientifica Trust has funding available for early career researchers and clinicians in training for endocrinology research and clinical delivery. The next application deadline is **31 December 2021**. Visit [www.bioscientificatrust.org/grants](http://www.bioscientificatrust.org/grants) for details and to apply.



## HORMONES OUR EXPERT-LED, MYTH-BUSTING PODCAST IS BACK

Building on the huge success of last year's debut, we welcome series two of our podcast.

'Hormones: the Inside Story' continues to examine the stories and science behind hormones, cutting through myths and misinformation, providing real facts and enabling everyone to make better decisions about their health.

Please help us by encouraging your family, friends, colleagues, schools, and anyone else, to tune in and learn about hormones in an informative, inquisitive and fun way!

Head to [www.yourhormones.info/podcasts](http://www.yourhormones.info/podcasts), or simply search for 'Hormones: the Inside Story' on your app of choice.

## HELP IMPROVE MEDIA REPORTING

Become a Society Media Ambassador and share your expertise to help improve science and health reporting in the media. Media Ambassadors work alongside the Society's Press Office to provide accurate and responsible media reporting of endocrinology-related topics. Find out more in our free guide at [www.endocrinology.org/engaging-with-the-media](http://www.endocrinology.org/engaging-with-the-media).

## REFLECTING ON A CHALLENGING YEAR



As we begin to review our many achievements during 2021, it's a good time to reflect on and revisit some of the remarkable triumphs and advances that were accomplished during the exceptionally challenging 2020 in our *Year in Review*.

See [www.endocrinology.org/reports](http://www.endocrinology.org/reports).

## HOT OFF THE PRESSES

Our 2022 Medallists and Awardees have just been announced. Join us in congratulating them and watch out for more details on their achievements and upcoming lectures in the spring 2022 issue. Find out who they are at [www.endocrinology.org/news](http://www.endocrinology.org/news).

## PROTECT ESSENTIAL DRUG SUPPLIES FOR THE NHS

You can sign a petition in support of establishing a national UK manufacturer of essential, off-patent, generic medicines within the NHS. Making these medicines at close to production cost can introduce competition to prevent the unethical practice of 'price gouging'. Learn more and sign the petition at <https://petition.parliament.uk/petitions/593723>.



## SOCIETY CALENDAR

25-27 April 2022  
**ENDOCRINE ACADEMY: CLINICAL UPDATE & ENDOCRINE NURSE UPDATE**  
Birmingham, UK

2022  
**NATIONAL TRAINING SCHEME: USE OF RADIOIODINE IN BENIGN THYROID DISEASE**  
Physical & Virtual, UK

2022  
**NATIONAL CLINICAL CASES**  
Physical & Virtual, UK

14-16 November 2022  
**SfE BES 2022**  
Harrogate, UK

[www.endocrinology.org/events](http://www.endocrinology.org/events) for full details



## GRANT AND PRIZE DEADLINES

9 March 2022  
**TRAVEL GRANT**

9 March 2022  
**SUMMER STUDENTSHIP GRANT**

16 March 2022  
**PATIENT SUPPORT GROUP GRANT**

23 March 2022  
**PUBLIC ENGAGEMENT GRANT**

6 April 2022  
**PRACTICAL SKILLS GRANT**

4 May 2022  
**EARLY CAREER GRANT**

4 May 2022  
**EQUIPMENT GRANT**

18 May 2022  
**ENDOCRINE NURSE GRANT**

18 May 2022  
**MEETING SUPPORT GRANT**

[www.endocrinology.org/grants](http://www.endocrinology.org/grants) for full details of all Society grants and prizes

# HOT TOPICS

## SOCIETY FOR ENDOCRINOLOGY OFFICIAL JOURNALS

Society members have free access to the current content of *Journal of Endocrinology*, *Journal of Molecular Endocrinology*, *Endocrine-Related Cancer* and *Clinical Endocrinology* via the Members' Area on the Society website, [www.endocrinology.org](http://www.endocrinology.org). *Endocrine Connections*, *Endocrinology*, *Diabetes & Metabolism Case Reports* and *Endocrine Oncology* are open access and free to all. Publishing in *Endocrine Oncology* is currently free.



### JOURNAL OF ENDOCRINOLOGY

#### Special issue marking 100 years since the discovery of insulin

Guest Editors, Professor Decio Eizirik and Dr James Cantley, have commissioned a series of reviews from leaders in the field. Professor Eizirik explains, "The discovery of insulin was one of these rare events in the history of medical research that acutely changed a mortal disease into a chronic but treatable one. Unfortunately, the treatment of diabetes remains a challenge, and many patients eventually develop chronic complications associated with the disease that decrease both their life span and life quality. A central component of nearly all forms of diabetes is a relative or absolute pancreatic beta cell deficiency; the present series

of articles provides a timely overview on how beta cells function or fail, and lead to disease.

"We hope that this will trigger additional research that may translate into novel therapies to preserve beta cells in diabetes. None of these subsequent steps will be 'spectacular jumps' as the discovery of insulin, but step by step they will improve the life of diabetic patients and, hopefully, one day, allow prevention of the disease in many of them."

Watch the introductory video and read the issue at <https://joe.bioscientifica.com/page/100-years/100-years-of-insulin-a-special-collection>.

### JOURNAL OF MOLECULAR ENDOCRINOLOGY

#### 25 years of oestrogen receptor- $\beta$

Warner *et al.* review the history of the oestrogen receptor beta isoform (ER $\beta$ ), discovered in 1996 by Jan-Åke Gustafsson's team at Karolinska Institutet, Stockholm, Sweden. The discovery of ER $\beta$  helped to resolve a novel endocrine pathway in the prostate, by elucidating that the potent androgen dihydrotestosterone could be metabolised to the oestrogenic metabolite 5 $\alpha$ -androstane-3 $\beta$ ,17 $\beta$ -diol (3 $\beta$ -Adiol). 3 $\beta$ -Adiol was found to be an agonist of the novel ER $\beta$  and, in experimental models, could oppose androgen signalling, making it a potential target for prostate cancer treatment.

Initially, ER $\beta$  was thought of as a 'vestigial receptor' because it had no proliferative effects in the uterus, although knockout studies suggested it was required for fertility in females. Functional roles in the prostate and breast have

only been confirmed as recently as 2020, following the complete removal of the receptor that had eluded previous methods for generating ER $\beta$  knockout mice.

A number of natural and synthetic ligands to ER $\beta$  have been identified and have been effective at improving pathologies in rodent models of neurodegenerative diseases. Translation of these studies has been hampered by differences in ER $\beta$  signalling in rodents and humans. This is primarily due to the presence of receptor splice variants in humans/primates that are absent in rodents. Thus, better understanding of ER $\beta$  signalling and the role of splice variants in humans is required before the full potential of this promising therapeutic target can be realised.

Read the full article in *Journal of Molecular Endocrinology* **68** R1–R9

### ENDOCRINE-RELATED CANCER

#### Highly accurate NETest for paragangliomas and pheochromocytomas

Pheochromocytomas (PHEOs) and paragangliomas (PGLs) are neural crest-derived tumours that are most commonly found in the adrenal glands. PHEOs/PGLs represent diagnostically challenging and complex neuroendocrine tumours (NETs) which have limited or technically complex biomarker tests for diagnosis.

Pacak *et al.* tested the diagnostic utility of a NET-specific 51-marker blood assay (NETest) in a prospective, age-/gender-matched case-control study which included 81 patients with PHEOs/PGLs and age-/gender-matched controls

( $n=142$ ). Target transcripts (mRNA) were isolated from whole blood, and gene expression was evaluated using multi-algorithmic artificial intelligence-based analysis.

In this prospective study, a blood-based (liquid biopsy) multigenomic assay was effective (accuracy >99%) as an *in vitro* diagnostic measure for PHEOs/PGLs. NETest is therefore likely to have clinical utility in the diagnosis and management of PHEO/PGL patients.

Read the full article in *Endocrine-Related Cancer* **28** 731–734

### CLINICAL ENDOCRINOLOGY

#### Haemodynamic instability in laparoscopic adrenalectomy for pheochromocytoma

Following on from the entertaining and thought-provoking debate on preoperative blockade for pheochromocytoma/paraganglioma during SfE BES 2021, this paper caught my eye.

Takeda *et al.* describe a case series of 68 patients undergoing a laparoscopic adrenalectomy for pheochromocytoma, looking at haemodynamic instability (HDI; defined as systolic blood pressure  $\geq 200$  or  $< 80$  mmHg). Out of 68 patients, 25 had HDI, with 19 patients requiring pressor use postoperatively. Factors associated with HDI were age, higher levels of metanephrines and the presence of diabetes mellitus. Diabetes mellitus was associated with postoperative pressor use.

The authors did not describe preoperative preparation being associated with HDI, although the regimens used were not the same as we might use in the UK. Nor was there a comment on preoperative filling or volume status.

These data suggest that it is not just the blockade that determines outcome. Patients with stiffer arteries that are less able to constrict when anaesthesia starts, or once the tumours are removed, may explain these findings in part. The study suggests that  $\alpha$  and  $\beta$  blockade are not the only things to focus upon when preparing and managing patients perioperatively. As we all know, having a skilled anaesthetist is key, and maybe this is our learning point: a team approach with close working between endocrinologist, surgeon and anaesthetist should be top of our list for a successful surgical outcome.

Read the full article in *Clinical Endocrinology* **95** 716–726



**ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS**

**Graves' disease, HIV and late immune reconstitution inflammatory syndrome after antiretroviral therapy**

Ludgate and colleagues report the case of a 40-year-old woman who developed both adrenal insufficiency and Graves' disease in the course of HIV diagnosis and antiretroviral therapy.

In particular, the Graves' disease was thought to arise as part of an immune reconstitution inflammatory syndrome (IRIS), in response to cryptococcal infection. The patient had no family or personal history of thyroid autoimmunity, and previous thyroid imaging and biochemistry had been normal. Interestingly, the patient underwent a change in antiretroviral therapy two years before the diagnosis of Graves' disease (with subsequent increase in CD4 count). The authors speculate that expansion of the naïve CD4+ T cell compartment may have triggered the (delayed) Graves' disease presentation. At the time of writing, standard Graves' disease treatment (carbimazole) was proving effective.

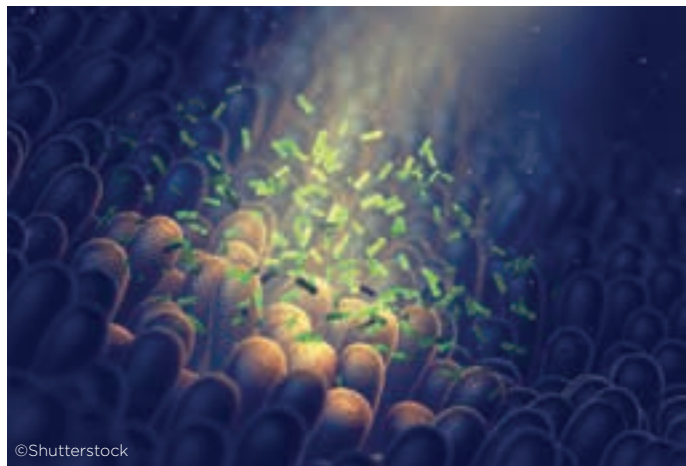
Whilst the authors cannot exclude the Graves' disease arising independently of HIV infection and treatment, this report is a useful reminder for both endocrinologists and infectious disease physicians of the endocrinopathies that can be associated with HIV and antiretroviral therapy, and of the need to be vigilant for signs and symptoms.

Read the full article in *Endocrinology, Diabetes & Metabolism Case Reports* doi: 10.1530/EDM-21-0094



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**ENDOCRINE CONNECTIONS**



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**Intestinal flora and gestational diabetes mellitus**

Gestational diabetes mellitus (GDM) is a disorder featuring high blood sugar that develops during pregnancy. As such, its occurrence is often associated with metabolic disorders, inflammatory activation and a loss of insulin sensitivity. Gut microbial dysbiosis (disruption of the microflora) has been linked to GDM, with a number of metagenomic studies describing changes to microbiota in pregnant women.

Su *et al.* assessed 122 pregnant women divided into two groups according to their body mass index (BMI). They found that 27 of the 98 subjects who had a BMI <24kg/m<sup>2</sup> had GDM, while 7 of the 24 women with a BMI >24kg/m<sup>2</sup> had GDM.

In women without GDM, the composition of the intestinal flora was unchanged and independent of BMI. Women with GDM in the higher BMI group showed a gut flora that was significantly different from those with GDM in the lower BMI group. Examination revealed that women in the higher BMI group with GDM had an increased relative abundance of *Bacteroidetes* and lower abundance of *Firmicutes*.

This study suggests that supplementary probiotics may have utility in reducing the risk of GDM.

Read the full article in *Endocrine Connections* **10** 1366–1376

**ENDOCRINE HIGHLIGHTS**

A summary of papers from around the endocrine community that have got you talking.

**Muscle repair after physiological damage relies on nuclear migration**

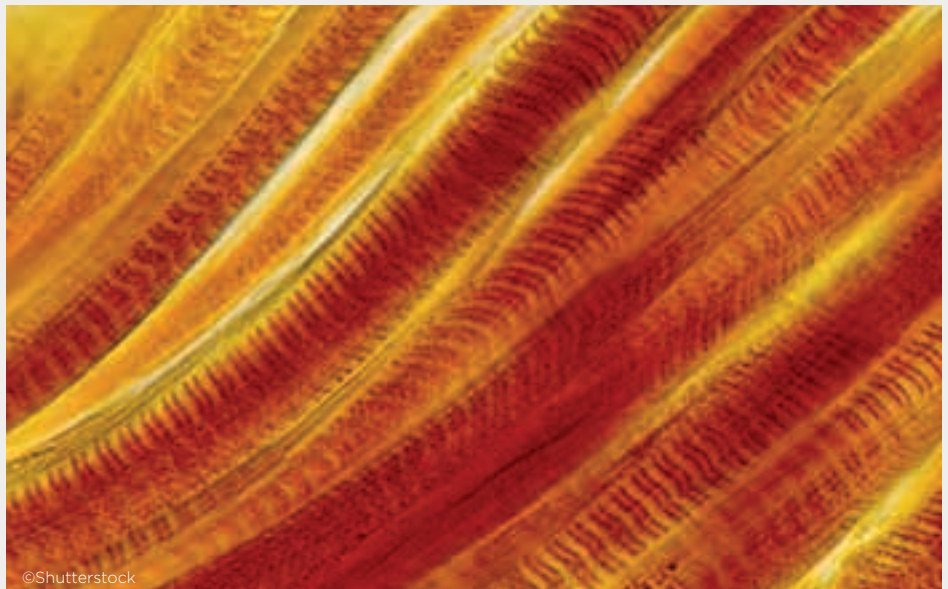
During physical challenge such as exercise, or even during less intense activity, skeletal muscle tissue can be subject to minor damage such as microtears. Regeneration by satellite cells residing in the muscle has been studied for decades.

However, a new study by Roman *et al.* describes a novel mechanism for muscle repair involving migration of the myocyte nuclei that is apparently independent of satellite cell function.

The authors found that, upon injury, the cell nuclei migrate to the site and facilitate restoration of the contractile machinery. Specifically, nuclei were able to rapidly deliver the mRNA necessary to generate the proteins crucial for muscle repair.

This is an important finding for those investigating muscle physiology. However, this work also delivers more fundamental knowledge with respect to wider understanding. For example, studies investigating nuclear movement now have a role for this mobilisation. Its occurrence within other tissue and cell types remains to be elucidated.

Read the full article in *Science* **374** 355–359



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# DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE: THE GLUCOCORTICOID HYPOTHESIS

WRITTEN BY KERRI DEVINE AND REBECCA M REYNOLDS



Epidemiological research carried out in the late 1980s and 1990s revealed a link between low birthweight and the onset of metabolic disorders, including obesity, hypertension and type 2 diabetes, in adulthood.

To explain this observation, in 1993, David Barker proposed that a fetus exposed to certain adverse factors during critical points in its development will make adaptations which result not only in restricted growth (and hence small birth size), but in permanent physiological changes, for example to blood vessel or endocrine functions.<sup>1</sup> These changes may have a survival advantage for the fetus, but are harmful in the long term, hence linking the early life environment with adult disease.

Barker believed this ‘developmental programming’ was driven by poor maternal nutrition, but decades of subsequent animal and observational studies have since expanded the potential underlying mechanisms to include a range of preconceptual, periconceptual and other intrauterine exposures. Excessive exposure to glucocorticoids in the womb is proposed as a key underpinning mechanism.

## GLUCOCORTICOIDS IN PREGNANCY

Levels of cortisol – the primary stress hormone produced by the adrenal gland – typically rise threefold in the human mother during pregnancy. The fetus is usually protected from this steroid surge by the actions of a placental enzyme (called 11 $\beta$ -hydroxysteroid dehydrogenase type 2, or 11 $\beta$ -HSD2) which inactivates glucocorticoids. Consequently only 10–20% of maternal cortisol transfers.

A rise in maternal cortisol in response to ‘stress’, or any small reduction in enzyme function, would result in a significant increase in circulating fetal glucocorticoid.

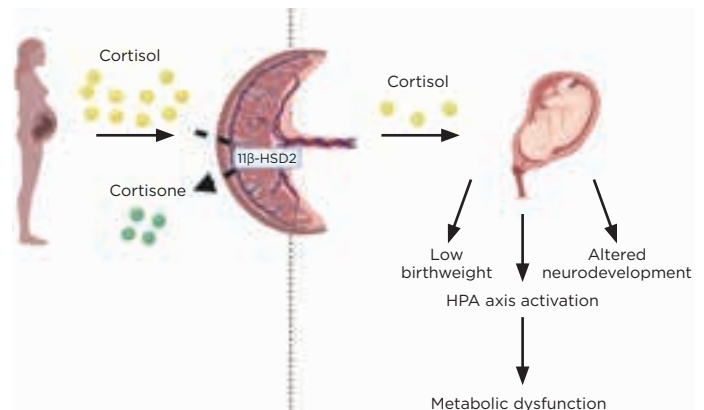
*‘Children whose mothers were treated with glucocorticoids during pregnancy have higher blood pressure and insulin resistance in adolescence and early adulthood.’*

## IMPACT OF HIGH GLUCOCORTICOID LEVELS

The ‘glucocorticoid hypothesis’ of fetal developmental programming was conceived when rodents lacking this enzyme (and therefore with high glucocorticoid transfer across the placenta) were noted to have smaller offspring.<sup>2</sup> Similarly, humans with lower placental 11 $\beta$ -HSD2 function, and those with the very rare homozygous 11 $\beta$ -HSD2 mutation, have lower birthweights than siblings. Further animal studies confirmed that greater placental steroid transfer (either due to maternal steroid administration or inhibition of 11 $\beta$ -HSD2) resulted in offspring that were not only smaller, but also, importantly, developed hypertension, altered fat metabolism and other features of the ‘low birthweight baby’ phenotype.

## MECHANISM OF ACTION

This enhanced glucocorticoid exposure during development appears to have long term effects on glucocorticoid regulation. The plasma



Maternal blood cortisol (yellow circles) reaches the placenta where it is partially metabolised by 11 $\beta$ -HSD2 into the inactive cortisone (green circles). An increase in cortisol transfer to the fetus (due to increased maternal levels, or reduced inactivation) results in low birthweight, long term activation of the HPA and alterations in development of the limbic system. This links the *in utero* environment with adult health and disease.

Figure created with BioRender.com

concentration of glucocorticoids is controlled by the hypothalamic-pituitary-adrenal (HPA) axis, and low birthweight animals and humans have a change in the ‘sensitivity’ of the axis towards higher glucocorticoid concentrations. Rats which have been exposed to steroids *in utero* have high basal glucocorticoid levels throughout life, for example.

Maternal liquorice consumption in pregnancy has been used as a novel marker of fetal cortisol exposure, since liquorice contains a natural 11 $\beta$ -HSD2 inhibitor (glycyrrhizin). Children whose mothers had high liquorice intake during pregnancy, compared with those with none, had greater and brisker salivary cortisol production on waking.<sup>3</sup> Long term population cohort studies have demonstrated that those with lower birth weights have higher cortisol concentrations, as well as enhanced cortisol production to stimulus, in early and late adulthood. This again suggests a lifelong alteration to the axis.

It is intuitive to endocrinologists that dysregulation of the HPA axis results in hypertension, obesity, insulin resistance and cardiovascular disease, as this is typical of Cushing’s syndrome. We have already demonstrated the principle that greater fasting cortisol in humans is associated with a variety of adverse metabolic features, including hypertension, hyperglycaemia and dyslipidaemia.<sup>4</sup> Furthermore, in cohort and cross-over studies, we have linked these adverse features with both low birthweight and HPA axis activation.<sup>5</sup> Children whose mothers were treated with glucocorticoids during pregnancy have higher blood pressure and insulin resistance in adolescence and early adulthood.<sup>6,7</sup>

## OVERCOMING CHALLENGES IN ANALYSIS

One of the key limitations in this field results from the challenges of measuring cortisol exposure in pregnancy, with many factors, such as time of sample collection and several maternal characteristics, leading to large variations in measurements of cortisol in blood during pregnancy.<sup>8</sup> One potential way to overcome this is through measurement of cortisol in hair, with 1cm of hair representing a month of cortisol exposure. We measured cortisol in maternal hair samples collected at the time of birth, representing cortisol exposure in the last three months of pregnancy.<sup>9</sup>

The newborn babies underwent brain scans using magnetic resonance imaging (MRI) to examine the structure and connections of the amygdala, the part of the brain that processes emotions. We found that being exposed to higher cortisol levels in the womb affected babies in different ways based on their sex: boys showed alterations in the

fine structure of their amygdala, while girls displayed changes in the way that that brain region connected to other neural networks. Thus, cortisol exposure in the womb also appears important for offspring neurodevelopment.

A further limitation is the observational nature of the available data, and the challenge of demonstrating a causative role for glucocorticoids in human studies. The Early Growth Genetics (EGG) Consortium has made major advances using advanced statistical methods (Mendelian randomisation) to demonstrate how maternal and fetal genetic effects may explain some of the observed associations between size at birth and adult diseases, including hypertension and type 2 diabetes. The knowledge that morning cortisol is genetically determined<sup>10</sup> paves the way for further exploration of the ‘glucocorticoid hypothesis’.

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## KERRI DEVINE AND REBECCA M REYNOLDS

Clinical Research Fellow and Professor of Metabolic Medicine, Centre for Cardiovascular Science, Queen’s Medical Research Institute, Edinburgh

# GDF15: SOMATIC DISTRESS, APPETITE AND AVERSION

WRITTEN BY TONY COLL



Over the last two decades, the peptide growth differentiation factor 15 (GDF15) has been associated with a wide variety of disease states. Although an elevation in circulating GDF15 was clearly a marker of poorer prognosis and disease severity, there remained much uncertainty around the mechanism and true pathophysiological role.

The identification in 2017 of its cognate receptor, GFRAL, in discrete areas of the brainstem, catapulted this hormone back into the limelight. It is a stress-regulated hormone with a potent effect on appetite, body weight and sickness behaviour, so reagents that influence the GDF15–GFRAL axis have real potential to enter the clinical arena.

Our current understanding of the biology of GDF15 comes to us after a long period of iterative groundwork, where a gradual accrual of evidence quietly enabled the great leap forward. In the late 1990s, Sam Breit’s group first identified a peptide termed ‘macrophage inhibitory cytokine-1’ in a cellular model of macrophage activation. Through undertaking related work, several other groups isolated the same molecule as being a member of the transforming growth factor- $\beta$  superfamily, with a variety of names applied, until GDF15 was more universally adopted.

## A MARKER OF CELLULAR STRESS

GDF15 is expressed at relatively low levels in the basal state in most tissues in the body. It is synthesised as a larger propeptide, which goes on to be processed into the bioactive homodimer found in the circulation. In healthy individuals, circulating levels run somewhere between 200 and 1,200pg/ml; they increase with chronological age.

The consensus from both human and murine model studies is that, in the face of a balanced diet, GDF15 does not appear to have a role in day-

*‘So, can we perhaps think of GDF15 not so much as one of the housekeepers, but more as a loyal watchman, primed and ready to signal danger and attack from wherever it may arise?’*

to-day metabolic regulation. In contrast, whenever tissues are injured or under duress, GDF15 expression and production are markedly upregulated. This stress can come from diverse angles, from intense exercise and altitude-associated hypoxia through to an amino acid-imbalanced diet and environmental toxins. One other fascinating scenario is that of pregnancy. GDF15 is highly expressed in the placenta and, even in normal pregnancy, maternal circulating levels rise rapidly during the first trimester and remain elevated until delivery.

## GDF15 AND DISEASE

Elevated circulating GDF15 levels are recognised in a wide variety of disease states, including a number of cancers, heart failure and renal disease. In acute critical illness, levels can exceed 20,000pg/ml. Some of the

highest concentrations recorded in any human disease (over 60,000pg/ml) were seen in patients with thalassaemia.

Initial studies in transgenic murine models repeatedly demonstrated that GDF15 was able to reduce food intake and bring about body weight loss. They showed that this was, as is so often the case with blood-borne mediators, probably through regulatory centres in brain. These earlier suspicions were proven to be correct in 2017, when a cluster of reports showed convincingly that GDF15's robust and dose-dependent ability to reduce food intake came about through action at the GFRAL receptor specifically expressed in the discrete 'chemoreceptor trigger zone' areas of the brainstem.

### APPETITE AND SICKNESS BEHAVIOUR

Now that the pathway was clear, a slightly revised view of GDF15's function emerged that still encompassed the irrefutable signals arising from the study of human populations with disease.

GDF15 could now be seen to be rather more than a biomarker. It was recognised as a key player in the allostatic response to illness. The stereotypical response seen in illness is typically one of lost appetite and food aversion that feels quite different from comfortable satiety. Again, animal studies proved highly informative in defining a role for GDF15 in these features of sickness behaviour. Indeed, there is also emerging evidence that GDF15 may play a role in the highly debilitating syndrome of hyperemesis gravidarum seen in some pregnancies.

Furthermore, although an acute rise in glucocorticoid in the face of severe somatic stress is well known to us all, work from our lab has shown that GDF15 can potently and rapidly activate the hypothalamic-pituitary-adrenal axis in rodents, highlighting this as an endocrine circuit in the 'chemical defensible' necessary to defend against toxin stress.

### CLINICAL APPLICATIONS

Circulating GDF15 is also increased by metformin. Our work, and that of others, has shown the effects of metformin on body weight in animals on a high fat diet to be mediated through a metformin-induced rise in GDF15. We have also identified the gastrointestinal tract as a major site of metformin-induced GDF15 expression.

Anorectic agents based on other gut-derived anorexigens like glucagon-like peptide-1 are now in routine practice, so could a similar picture play out for

GDF15 analogues in the treatment of obesity? While there are certainly such agents under active study that show great promise in reducing food intake, it is perhaps too early to know if they can progress to the therapeutic sweet spot of efficacy, safety and tolerability.

At the other end of the spectrum, blocking GDF15 action in conditions where anorexia and weight loss are problematic also makes sense. In the arena of cancer medicine, the use of the widely utilised, platinum-based cytotoxic agent cisplatin can be limited by its side effects, such as anorexia and emesis. Importantly, cisplatin elicits a strong rise in GDF15. In some exciting preclinical studies, antibody-directed neutralisation of GDF15's action is able to reduce emesis, increase food intake and prevent cisplatin-induced weight loss, suggesting GDF15 neutralisation may be a good additive step in chemotherapy treatment regimens.

### CONCLUSION

So, can we perhaps think of GDF15 not so much as one of the housekeepers, but more as a loyal watchman, primed and ready to signal danger and attack from wherever it may arise? Anthropomorphising hormones may be too trivial, but what is clear is that studies of this fascinating hormone have led to clinically relevant insights into serious problems, and it looks like there is much more to come.

### ACKNOWLEDGEMENTS

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### TONY COLL

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Submit yours to [media@endocrinology.org](mailto:media@endocrinology.org)



# REPLACEMENT AND THERAPEUTIC GLUCOCORTICOIDS: TIME FOR A CHANGE

WRITTEN BY DAVID W RAY



Glucocorticoids are essential for life and, before the synthesis of cortisone, a diagnosis of adrenal failure was a death sentence. Replacement and therapeutic use of glucocorticoids accelerated rapidly, driven by the massive impact their use had on patients. In many instances, the effects were so dramatic that no clinical trials were done, beyond gazing in wonder at the transformation in the recipient.

Following the enthusiastic roll out of glucocorticoid treatment, mainly for people with inflammatory diseases, it became clear that the glucocorticoids were a double-edged sword, with a spectrum of severe and irreversible side effects. Even then, no trials were performed to formally assess the adverse effects and therapeutic benefits, in the sense that we would now require trial evidence before drug approval by regulatory authorities.

In order to retain the therapeutic benefits of glucocorticoids for management of inflammatory diseases, and to replace missing glucocorticoid synthesis in adrenal insufficiency or congenital adrenal hyperplasia, efforts have focused on new, synthetic molecules with selective modes of action. These act either to limit activation of the mineralocorticoid receptor, such as prednisolone or dexamethasone, or in a way analogous to the partial oestrogen receptor agonists used to treat breast cancer. In addition, attention has switched to formulation of the compounds for local use, such as inhaled glucocorticoid, or topical application to the eye, skin etc. Finally, the role of timing of administration has been explored.

## MECHANISM OF ACTION

In order to come up with better glucocorticoid therapeutics, it would help to understand how these compounds work. Although the glucocorticoid receptor (GR) was cloned in 1987, and much is known about how ligand activation of the receptor drives phenotypic change, there are gaps in our knowledge. It is possibly because of these gaps that the field has fallen behind the progress seen with other, related receptors, such as oestrogen and androgen receptors and peroxisome proliferator-activated receptors.

*'The focus on therapeutic glucocorticoids has meant that rather little attention has been paid to replacement glucocorticoids...'*

Briefly, activated GR binds to target sequences in DNA, to switch on gene transcription and thereby change the proteome of the cells, and so its function, and that of the whole person. As the GR is expressed ubiquitously, this explains why topical application of the drugs is a good approach, to limit target effects.

The focus on therapeutic glucocorticoids has meant that rather little attention has been paid to replacement glucocorticoids, which are the realm of the clinical endocrinologist. These are rare conditions, there is little big pharma interest, and trials can be hard to recruit to.

What do we know about physiological glucocorticoids? Strikingly, endogenous production of glucocorticoids lies under control of multiple systems, resulting in wide variations in measured plasma concentrations during the course of a day. This is why dynamic or stress tests are used in the clinic to assess adrenal production of glucocorticoids. Glucocorticoids are secreted in discrete pulses into the circulation, with the frequency of pulses varying through the day to result in a marked diurnal change in plasma concentrations, with the peak levels achieved before waking. Glucocorticoid production is also stress responsive and starvation responsive, driving mobilisation of energy substrates.

It turns out that time of day also affects how tissues respond to glucocorticoids. So we can see a coincident model with time-dependent changes in glucocorticoid production, and also variation in the amplitude and spectrum of responding genes through time. This is more complex than the conventional models acknowledge.

*'...there is potential from the new biology of circadian endocrinology to drive greater benefits from this drug class and drug target.'*

## THERAPEUTIC OPPORTUNITIES

This variation also opens up the possibility of using timing to dial up greater disease sensitivity, target the spectrum of glucocorticoid effects, and limit off-target actions. For example, replicating the pulsatile secretion of endogenous glucocorticoids, with changes in pulse frequency through the day, will mimic the natural pattern and may improve well-being in people reliant on replacement steroid (see page 10 for Richard Ross's account of the development of Chronocort). In addition, targeting administration of therapeutic glucocorticoid to the time window when the disease is most likely to respond may allow greater efficacy or dose-sparing to be achieved.

The explanation of why the time of day matters is now becoming clear. The operation of a circadian clock within all cells of the body is fundamental to health, driving 15–20% of metabolic circuits. Core circadian clock component proteins are capable of direct interaction with the GR to change its function. In this way, the cell can interpret the incoming glucocorticoid signal in the context of the time of day. This is achieved both by modifying how the GR can activate gene transcription, and also by specifying which site in the genome the GR can bind to.

As components of the circadian clock can be affected by light, behaviour and feeding in terms of physiological change, and now can be directly targeted by new classes of drug-like molecules, this interface between the clock and glucocorticoid action is very exciting therapeutically. Further complexity is suggested by observations that obesity, and fat-loading of the liver, may introduce further control of how the GR works, potentially pointing to new mechanisms explaining the altered physiology seen in obesity.

Although therapeutic glucocorticoids have been around for more than 70 years, there is potential from the new biology of circadian endocrinology to drive greater benefits from this drug class and drug target. The combination of new molecules, new formulations and new administration paradigms offers new hope for patients. As more than 1% of the population have a regular, repeat prescription for a glucocorticoid, this is a huge target group of people, who stand to benefit. Exciting times for an old drug target.

DAVID W RAY

Professor of Endocrinology, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford

# RESTORING DIURNAL RHYTHMS IN CONGENITAL ADRENAL HYPERPLASIA

WRITTEN BY RICHARD J M ROSS



In 2000, the Society for Endocrinology recommended an audit of adults with congenital adrenal hyperplasia (CAH). This led to a publication in 2010 by the CaHASE consortium reporting poor health outcomes in CAH, and highlighting the need for better glucocorticoid replacement. In 2021, Diurnal Ltd launched Chronocort (brand name Efmody), an oral modified-release hydrocortisone capsule that reproduces the cortisol circadian rhythm to address the unmet need in patients with CAH. This is the story of Chronocort's development.

In 1999, I attended the Endocrine Society meeting in San Diego, USA, on my way to a sabbatical in Sydney, Australia (I can highly recommend sabbaticals!). At Sheffield, we were doing research on hydrocortisone replacement. On a boat trip in San Diego harbour, I remember talking to a senior sales manager in big pharma and trying to persuade him to invest in a programme for a delayed and sustained release formulation of hydrocortisone that we had modelled to replace the cortisol circadian rhythm.<sup>1,2</sup> There were two things I learnt from this boat conversation...

1. Talking to sales managers about research is a waste of time as they are happy to listen but, on the whole, have no way of supporting research.
2. Big pharma rarely invests in early stage programmes.

Mind you, it took me five years before I got the message. On return from my sabbatical, at the start of the millennium, I was invited to join the Society for Endocrinology's Clinical Committee. At my first meeting, Howard Jacobs said, "No one knows how to manage adults with CAH, so should we undertake an audit?" Being the new bug, I put up my hand to lead the audit. We quickly realised there were no standards and little evidence so, instead of an audit, we set up research.

## A PRODUCTIVE COLLABORATION

This was the start of the CAH Adult Study Executive (CaHASE), a consortium of academic centres across the UK. The research was funded

by the Clinical Endocrinology Trust and supported by the Society for Endocrinology. It proved a highly productive collaboration.<sup>3</sup>

In 2010, CaHASE published a landmark paper demonstrating poor health outcomes in adults with CAH: in large part due to inadequate glucocorticoid replacement with either too little or excess glucocorticoid exposure.<sup>4</sup> The work was confirmed by other cohort studies showing patients with CAH have increased mortality, obesity, osteoporosis and cardiovascular risk factors and reduced fertility.<sup>5</sup>

## ADDRESSING AN UNMET NEED

Whilst the CaHASE consortium was collecting data on health outcomes in CAH, at Sheffield, we were looking to address the unmet need for a better glucocorticoid replacement. We had determined that we needed a delayed and sustained formulation of hydrocortisone, and the challenge was to identify a technology to make the formulation.

In 2004, Sheffield filed a patent and formed a spinout company: Diurnal Ltd. Diurnal licensed the patent to a company Phoqus. They had a technology based on photocopying that could make a bucket tablet with insoluble sides, which had hydrocortisone in the bottom in a sustained formulation, and a delayed release, eroding top coat. This Chronocort formulation provided proof of concept that delivering the overnight rise in cortisol would improve CAH control.<sup>6</sup> However, the Phoqus technology didn't provide reproducible results and Phoqus went in to administration. The lesson learnt was: it's not a great idea to combine a new drug idea with a new technology, as you double the risk of failure.

*'The over-riding lesson I learnt is "follow the science and keep going, as success comes from understanding why something doesn't work".'*

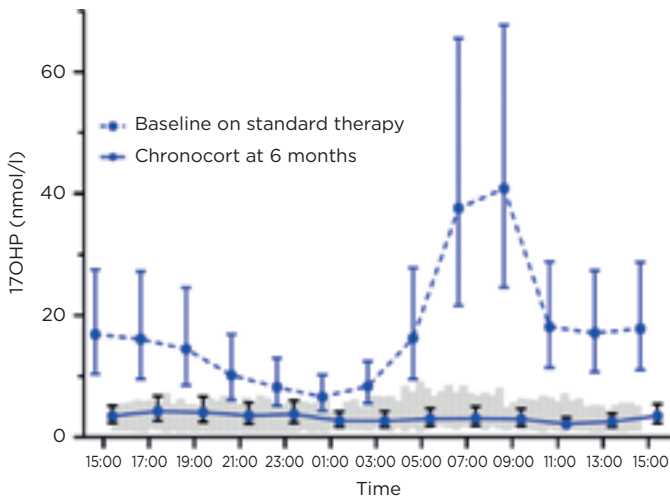
In 2008, Diurnal started its own programme to develop Chronocort using established multi-particulate technology (Figure 1). The first formulations used a delayed and sustained coating of hydrocortisone which, when tested in dexamethasone-suppressed healthy volunteers, gave the correct profile

but very poor bioavailability. We then tried only a delayed release layer and found it had both the right profile and the relative bioavailability to immediate release hydrocortisone.<sup>7</sup> This Chronocort formulation showed greatly improved biochemical CAH control at phase 2 trial.<sup>8</sup>

We then undertook the first randomised controlled study of glucocorticoid replacement in patients with CAH. The phase 3 trial failed its primary endpoint because the prespecified endpoint obscured the benefit of Chronocort in the morning and early afternoon. Post-hoc analysis showed that Chronocort improved control of the main CAH biomarker 17-hydroxyprogesterone (17OHP) versus standard therapy (Figure 2). In the Chronocort safety extension study, 80% of patients showed good disease control on a median

Figure 1. Chronocort multi-particulate formulation.





**Figure 2.** 17OHP at baseline on standard treatment (dashed line), showing marked diurnal rhythm with high levels in the morning, and on Chronocort at 6 months (solid line), showing that Chronocort treatment normalises 17OHP levels. Grey shaded area is 17OHP in healthy controls. Reproduced in adapted form from Ghizzoni *et al.*<sup>10</sup> by permission

daily hydrocortisone dose of 20mg, which is an adrenal replacement dose of hydrocortisone.<sup>9</sup> Improved biochemical control on Chronocort was associated with the patient-reported benefit of improved energy and restoration of menses with six pregnancies in the 27 women of fertile age and improved sperm count and four partner pregnancies for men with CAH.

### APPROVAL OF CHRONOCORT

Chronocort was approved by the European Medicines Agency and the Medicines and Healthcare Products Regulatory Agency in 2021, and has been launched in Germany and the UK for the treatment of CAH patients of 12 years and older. Chronocort provides a rational, twice daily 'toothbrush' regimen with simplified monitoring, with morning 17OHP reflecting the night-time dose and afternoon 17OHP the morning dose.

The story of Chronocort development is one of peaks and troughs of success and failure. The over-riding lesson I learnt is 'follow the science and keep going, as success comes from understanding why something doesn't work'. Chronocort is an important advance in the therapy of CAH which we anticipate will improve the long term health outcomes of patients with this disease.

### RICHARD J M ROSS

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## TAKOTSUBO SYNDROME: THE ENDOCRINOLOGY OF CARDIOLOGY

WRITTEN BY LIAM S COUCH, ALEXANDER R LYON AND SIAN E HARDING

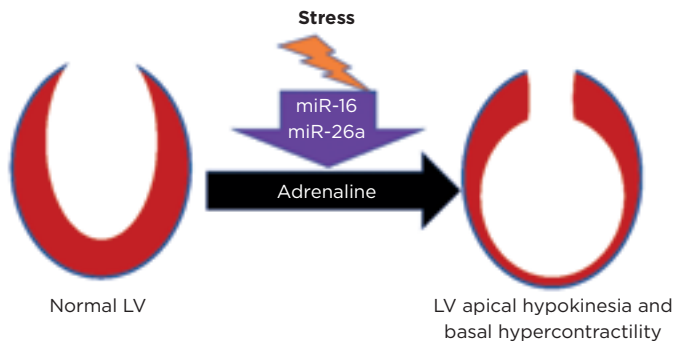
Takotsubo syndrome (TTS), also known as 'broken heart syndrome', is an increasingly recognised condition which represents a large overlap between endocrinology and cardiology. It is a severe, but reversible, acute heart failure that occurs following a catecholamine surge.

TTS patients present similarly to those with myocardial infarction (MI), with chest pain and ST-segment elevation on electrocardiogram. Critically, they are distinguished by imaging, with left ventricular apical hypokinesia with basal hypercontractility occurring in the absence of culprit coronary artery disease. This characteristic pattern led to the naming of TTS, with 'tako-tsubo' translating to 'octopus pot' in Japanese, which its morphology resembles.

TTS predominantly affects postmenopausal women, typically occurs following extreme physical or emotional stress,<sup>1</sup> and is thought to represent

5–6% of female patients presenting with suspected ST-elevation MI, with similar prognosis.<sup>2</sup> The profound contractile dysfunction in TTS causes serious complications, including cardiogenic shock, thrombi formation, left ventricular rupture, pulmonary oedema and arrhythmia. There is no evidence-based treatment for the acute or chronic management of TTS, therefore a greater understanding TTS pathogenesis is important.

Whilst the association of TTS with catecholamines is well evidenced, there is no single established pathophysiological mechanism. Endothelial dysfunction, direct catecholaminergic myocardial stunning, oestrogen



**Figure.** Prior stress may predispose to future TTS. Representation of the left ventricle (LV) showing TTS, with contractile dysfunction following adrenaline made more likely by prior neuropsychiatric stress. Reproduced under CC BY 4.0 Licence (<http://creativecommons.org/licenses/by/4.0>) from Couch *et al.*<sup>10</sup> <https://doi.org/10.1093/cvr/cvab210> ©2021 The Authors

deprivation and brain–heart interaction have all been identified as important in TTS.

#### CATECHOLAMINERGIC MYOCARDIAL STUNNING

There is good evidence that catecholamines play a causative role in TTS. TTS may occur secondary to medical conditions with elevated catecholamine levels, such as pheochromocytoma, acute subarachnoid haemorrhage and acute thyrotoxicosis, and, iatrogenically, following dobutamine stress echocardiography or adrenaline administration. Further, TTS is robustly induced in rodent and primate models with adrenaline.<sup>3,4</sup>

Whilst the  $\beta_1$ -adrenergic receptor ( $\beta_1$ AR) signals via the stimulatory  $G_{\alpha s}$  pathway, the pleiotropic  $\beta_2$ AR can signal via  $G_{\alpha s}$  or the inhibitory  $G_{\alpha i}$ . This limits the proarrhythmic and proapoptotic effects of  $G_{\alpha s}$  activity and shifts receptor coupling to  $G_{\alpha i}$  by a process known as stimulus trafficking or biased agonism. Consequently,  $\beta_2$ AR- $G_{\alpha i}$  is directly cardiodepressive.  $\beta$ ARs have the highest density in the ventricular apex,<sup>3</sup> and apical cardiomyocytes have significantly larger overall  $\beta$ AR and  $\beta_2$ AR responses than basal cardiomyocytes.<sup>3</sup> This results in circulating adrenaline more profoundly affecting the apex of the ventricle in extreme stress.

*‘Processing of emotions and subsequent ANS response to stress may be profoundly altered in TTS patients, and could explain the “gain” in the hypothalamic-pituitary axis that has previously been suggested.’*

$\beta_2$ AR- $G_{\alpha i}$  negative inotrope effects can be reversed by inhibition with pertussis toxin,<sup>3</sup> although this also increases mortality in preclinical models. Endomyocardial biopsy studies from patients with TTS show activation of downstream  $\beta_2$ AR- $G_{\alpha i}$  prosurvival pathways. Indeed, increased levels of G protein-coupled receptor kinase and  $\beta$ -arrestin have been identified in TTS patients,<sup>6</sup> and these proteins are required for  $\beta_2$ AR- $G_{\alpha i}$  stimulus trafficking to occur.

#### OESTROGEN DEPRIVATION

Given the increased incidence of TTS in postmenopausal women, the involvement of oestrogen withdrawal has, logically, been proposed. Oestrogen is cardioprotective via a multitude of mechanisms, including limiting sympathetic stimulation and activating  $\beta_2$ AR- $G_{\alpha i}$  signalling pathways. Circulating adrenaline is lower in women than men at baseline, as are urinary cortisol, adrenaline and noradrenaline, which rise with age. Interestingly, these hormones are reduced by hormone replacement therapy (HRT), suggesting regulation by oestrogen. Adrenergic-dependent gene expression changes are observed in rodent models of TTS and prevented by oestrogen supplementation.<sup>7</sup> The impact of HRT on TTS incidence and recurrence is not clear, and offers an interesting avenue for further investigation.

#### BRAIN–HEART AXIS

Given the implied importance of the autonomic nervous system (ANS) in TTS, and the close association of TTS with neuropsychiatric disorders, there seems to be a clear interaction between the brain and heart in TTS.

Alterations within the insula, limbic system and ANS-specific signalling networks have been noted in patients with TTS.<sup>8</sup> This suggests processing of emotions and subsequent ANS response to stress may be profoundly altered in TTS patients, and could explain the ‘gain’ in the hypothalamic-pituitary axis that has previously been suggested in TTS.<sup>1</sup>

MicroRNAs (miRNAs) have recently been identified that are linked to neuropsychiatric stress and can be used as biomarkers to distinguish TTS from ST-elevation MI and healthy controls.<sup>9</sup> A recent preclinical study increased expression of TTS miRs (miR-16 and miR-26a) *in vitro* and *in vivo*. This predisposed to catecholamine-induced negative inotropism in the left ventricular apex and positive inotropism in the left ventricular base, and TTS generation *in vivo* at lower adrenaline concentrations.<sup>10</sup> This raises the possibility of a pathophysiological link between pre-existing stress and TTS via these miRs, and that prior neuropsychiatric stress may prime the heart to be more vulnerable to future TTS generation in situations of high adrenergic stress (see Figure).<sup>10</sup>

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# EVENTS AND TRAINING IN 2022



The Society is proud to reintroduce physical events and training conferences, whilst continuing our educational online webinar series. Don't miss the opportunity to exchange knowledge and experiences with your peers! Discover more at: [www.endocrinology.org/events](http://www.endocrinology.org/events).

## Endocrine ACADEMY

25–27  
APR

Hilton Birmingham Metropole Hotel

We are excited to reconnect you with your colleagues this April, as Endocrine Academy returns for the first time since 2019, with the compelling Endocrine Nurse Update and the highly anticipated Clinical Update.

**Clinical Update 2022**, complemented by our Clinical Skills Webinar series, includes vital materials to help prepare you for the RCP Specialty Certificate Examination in Endocrinology and Diabetes.

**Endocrine Nurse Update** will provide fundamental information to update you on best practice and the latest methods in the field.

Endocrine Academy is also an excellent way to network with the wider endocrine community, so don't miss the opportunity to attend.

## National Training Scheme for the USE OF RADIOIODINE IN BENIGN THYROID DISEASE

2022

United Kingdom (Physical/Virtual)

An essential element of the new national training scheme: attend to apply for the ARSAC certification for iodine-131 administration for the treatment of benign thyroid disease. Further information on the event will be provided in due course.

## National CLINICAL CASES

2022

United Kingdom (Physical/Virtual)

National Clinical Cases 2022 will showcase ten oral communications covering a variety of clinical cases for trainees and consultants to discuss and dissect. National Clinical Cases creates the perfect setting for trainees to present their cases to established endocrinologists, which is why it is always over-subscribed, year-on-year. Further details on how to take part will be provided in due course.

## SfE BES 2022

14–16  
NOV

Harrogate Convention Centre

Save the date for our next SfE BES conference which is taking place in Harrogate in 2022! We look forward to continuing to bring you the best in endocrine research, the newest practice and latest clinical advances, whilst providing the opportunity to showcase your research to a global audience.

## 2022 ONLINE WEBINARS

We are pleased to announce the following webinar series will continue throughout 2022. Each webinar will be broadcast live and then available to stream on demand within the Members' Area of the Society website.

- Research Skills Webinars 2022
- Endocrine Nurse Skills Webinars 2022
- Clinical Skills Webinars 2022
- Career Skills Sessions 2022

# Endocrine excellence IN EDINBURGH



Our annual SfE BES conference was held in Edinburgh on 8–10 November. The event attracted more than 840 in-person attendees over 3 days for the very best clinical and scientific endocrine research from across the discipline, for the first time since 2019.

After all the disruption to the endocrine community since March 2020, it was fantastic to welcome so many of you back for a full conference programme, live in Edinburgh. We also understood that not everyone would be able to travel, so introduced a new on-demand registration option for attendees to access the best of the programme after the event.

**352**  
posters  
presented

**“**Excellent meeting which I thoroughly enjoyed; a real pleasure to attend in person.

**“**Really well organised, very interesting, loved the debate lecture.

**“**Excellent, excellent, excellent conference.

**36**  
oral  
communications

The programme included the presidential lecture, plenaries, medal lectures, oral communications, poster presentations, an interactive debate, applied physiology workshops, meet the expert sessions, 'what is new' sessions and our special 75th anniversary lecture, which celebrated our Society and discipline. We were honoured to welcome

Professor Jeffery Friedman, as our 75th anniversary lecturer and Nobel Laureate, Professor Sir Peter Ratcliffe, who delivered an outstanding presidential lecture. Structuring our symposia, meet the expert sessions, oral communications and poster sessions around the Endocrine Network topics was again successful at bringing these communities together for a more tailored conference experience.

Over  
**440**  
tweets used  
#SfEBES2021  
during the  
event



**“** A really superb meeting - the plenaries were exceptional. **”**



**404**  
abstracts  
submitted

On Monday evening, delegates finally had the chance to mingle with a socially-distanced drink and a nibble at the welcome reception, whilst some Early Career and Nurse Members had a night of frivolity at the Curry and Quiz. There was a real buzz of excitement, as teams competed to make the best endocrine organ models, get the most questions correct and dance their way to prizes!

The impressive National Museum of Scotland provided the venue for the conference dinner.

Amongst the grand setting, fabulous food and beautiful exhibits, delegates were able to have a dance and enjoy a long-awaited get-together!



**841**  
delegates  
attended

**Prizes and Awards**

Professor Rajesh Thakker  
University of Oxford &  
Professor Duncan Bassett  
Imperial College London

**REWARDING EXCELLENCE**

It's not all about the prestigious Medal Lecturers at the SfE BES conference, the best presentations of new research and clinical practice advances were also recognised with a selection of prizes awarded at the event.

**CLINICAL ENDOCRINOLOGY TRUST PRIZES**

**Top scoring clinical abstract:** Alexander Lewis and Richard Ross (EC1.3)

**Top scoring basic abstract:** Mariana Norton (EC1.4)

**Top nursing practice abstract:** Kerrie Grounds (P130)

**Annette Louise Seal Award (sponsored by Addison's Disease Self Help Group)**

**Winner:** Sherwin Criseno (P17)

**Runner up:** Lisa Shepherd (P133)

**Featured Clinical Cases Poster Prize (supported by Endocrinology, Diabetes and Metabolism Case Reports)**

**Winner:** Shailesh Gohil (CC5)

**567**  
registered  
users on the  
App

**ENDOCRINE NETWORK PRIZES**

**Best Oral – Adrenal and Cardiovascular:** Giulia Argentesi (OC4.2)

**Best Poster – Adrenal and Cardiovascular:** Emily Warmington (OP2.3)

**Best Oral – Bone and Calcium:**

Morten S Hansen (OC5.2)

**Best Poster – Bone and Calcium:**

Muhammad Fahad Arshad (OP5.1)

**Best Oral – Endocrine Cancer and Late Effects:** Claire Fletcher (OC2.5)

**Best Poster – Endocrine Cancer and Late Effects:** Rebecca Mile (OP6.4)

**Best Oral – Metabolism, Obesity and Diabetes:**

Phyllis Phuah (OC3.5)

**Best Poster – Metabolism, Obesity and Diabetes:** Lewis Spencer (and Georgios Dimitriadis) (OP4.2)

**Best Oral – Reproductive and Neuroendocrinology:** Layla Thurston (OC1.1)

**Best Poster – Reproductive and Neuroendocrinology:** Abigail Byford (OP3.2)

**Best Oral – Thyroid:** Steffen Mayerl (OC6.2)

**Best Poster – Thyroid:** George Pooley and Bronwyn Shishkin (OP1.4)



Richard Ross



Sherwin Criseno (l) & Lisa Shepherd (r)



Emily Warmington



Rebecca Mile



Steffen Mayerl



Shailesh Gohil



Lewis Spencer



Layla Thurston







“The quiz was fun and a great way to meet new people.”



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# BRINGING STEROID SAFETY TO THE MASSES



WRITTEN BY ANNA MITCHELL AND LOUISE WALKER

In endocrinology, we are acutely aware of the importance of steroid safety. Keeping our steroid-dependent patients safe and well is an important part of our day-to-day work and, in general, we all feel like we are pretty good at it. But we need to think beyond our own discipline.

For the Endocrinology Team in Newcastle upon Tyne, steroid safety is something of an obsession. We use a 'pop-up' electronic record alert for all steroid-dependent patients who attend endocrine outpatient clinics, and we register them as being steroid-dependent with their local ambulance trust. We aim to empower our steroid-dependent patients to manage their medications independently, to allow them to remain in control of their health and well-being.

The endocrine nurse specialists have a particularly important role to play here, in educating patients and anyone else who is interested. We offer intense support around the time of diagnosis and a 'little and often' approach thereafter, tailored to the patient's needs and wants. We usually start with a one-to-one training session, to go over steroid sick day rules in detail and how to administer an i.m. hydrocortisone injection in an emergency, and then follow-up refresher sessions. We regularly check that patients have a steroid card and an up-to-date injection kit, and we have also run successful group steroid education sessions. Our experience is that support is generally welcomed, and our patients know that we are just a phone call away to support them.

In August 2020, a National Patient Safety Alert (NPSA) was issued, with the aim of implementing a universal steroid emergency card to support early recognition and treatment of adrenal crisis in adults. In Newcastle, this prompted us to put together a 'steroid safety pack', containing the new steroid emergency card (pictured) and an information leaflet about steroid sick day rules. This was posted out to each of our steroid-dependent endocrine clinic patients. Within weeks of the alert being issued, our patients were sorted (and we felt a little bit smug about it).

## BEYOND ENDOCRINOLOGY

However, before the steroid safety packs had even landed on people's doormats, we reflected, as a team, upon the vast majority of people taking steroids who are at risk of adrenal insufficiency and adrenal crisis and who are not being seen in endocrinology clinics. For example, they are being seen by:

- GPs who prescribe long courses of prednisolone for polymyalgia rheumatica
- nephrologists who prescribe long term steroids for renal transplant recipients

- rheumatologists who administer regular intra-articular steroids for inflammatory arthropathies, and
- respiratory doctors who prescribe potent inhaled steroids in combination with short, repeated courses of prednisolone in chronic obstructive pulmonary disease.

Regardless of their underlying diagnosis or the managing team, it is a crucial safety measure to ensure that patients who receive exogenous steroids and are at risk of adrenal suppression are identified and given appropriate and consistent steroid safety advice. As endocrinologists, we are ideally placed to support our colleagues in implementing the NPSA widely, to bring steroid safety to the masses.

## A CATALYST FOR CHANGE

The NPSA has shone a spotlight on the wider issue of steroid safety as a concern for ALL steroid-dependent patients, not just the ones attending endocrinology clinics. It represented, and still represents, an opportunity to share our steroid safety expertise widely.

In Newcastle, the NPSA has been a real catalyst for change and service improvement. We have used it to start conversations with colleagues in other specialties, about their approaches to identifying people on exogenous steroids who are at risk of adrenal insufficiency. It has given us the chance to ask colleagues about the education they offer steroid-dependent patients (in addition to ensuring that they are all given a steroid emergency card).

These conversations have led to each specialty identifying a 'Steroid Lead' to champion steroid safety. When the Steroid Leads met (virtually, thanks to COVID), it was obvious that many of the challenges that people encounter when managing steroid-dependent patients are universal and not specialty-specific. So, on the back of the NPSA, we have created shared pathways, for example for safe steroid withdrawal, and shared resources, including generic sick day rules patient information leaflets, and a quick reference guide for managing acutely unwell steroid-dependent adults in hospital. This should lead to consistent, high quality care for steroid-dependent patients, regardless of who is managing them.

## A TOOL FOR ENGAGEMENT

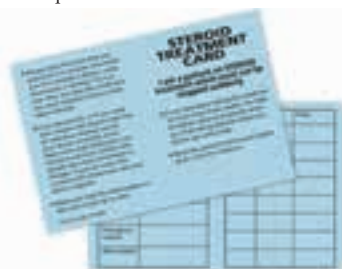
The NPSA has also been an excellent tool in engaging pharmacists in helping to identify patients who should be considered steroid-dependent. This helps ensure that they are given steroid emergency cards and sick day rules information with prescribed steroids. It has also acted as a focus for numerous education sessions on recognising adrenal crisis and managing it.

The NPSA has set in motion some very positive changes, and started some important conversations. We must capitalise upon the momentum gathered, to continue to keep steroid safety at the forefront of all clinicians' minds.

Steroid safety is not the sole preserve of endocrinologists. If we just talk to each other about steroid safety, then we are preaching to the choir. We need to break out of our echo chamber and actively engage our colleagues in recognising people who are at risk of adrenal insufficiency. In this way, we can support them in improving the safety of those patients, regardless of the clinic that they are attending.

**ANNA MITCHELL AND LOUISE WALKER**

Consultant Endocrinologist and Endocrine Nurse Specialist,  
Newcastle upon Tyne Hospitals NHS Foundation Trust



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# CORTICOSTEROIDS: LITTLE CHANGE?

WRITTEN BY GAVIN P VINSON

FIRST PUBLISHED IN ISSUE 94 (2009)

**‘For endocrine evolution is not an evolution of hormones but an evolution of uses to which they are put.’**

This perceptive comment was made by Peter Medawar in 1953 (*Symposia of the Society for Experimental Biology VII: Evolution* 320–338), and is the first published statement to this effect, though it was quickly adopted or assumed by others. It is somewhat irritating, since Medawar was a Nobel Prize-winning immunologist, not an endocrinologist at all, yet his statement was stunningly accurate, guided perhaps by Peter Krohn and Ian Chester Jones, from whom he sought advice.

There’s a remarkable parallel here with the classical concept of skeletal evolution, as interpreted from comparative anatomy. Here, the identity of the skeletal elements that, for example, make up the limbs of coelacanths, amphibia, reptiles, birds and terrestrial or flying mammals has been well understood by generations of undergraduates.

***‘Perhaps most striking is the number of uses to which prolactin has been put – osmoregulation in fish, water-seeking behaviour in certain amphibia, pigeon crop secretion and contributing to lactation in mammals.’***

There are many other examples, like the way in which the swim bladder was adapted on land to become an air-breathing lung. Indeed, fins that have become limbs and swim bladders that have become lungs are present in some species today, like lungfish, that are subject to variable availability of their ponds and lakes.

This illustrates the redesignation of structures to different functions as the environment or mode of life changes. It’s the product of the essential compromise between the ‘maximum parsimony’ and ‘no-redundancy’ concepts that perhaps might once have prevailed in evolutionary thought, before the baggage of unexpressed or otherwise redundant DNA in every nucleus was known.

But how fascinating that the same has occurred in hormones!

Perhaps most striking is the number of uses to which prolactin has been put – osmoregulation in fish, water-seeking behaviour in certain amphibia, pigeon crop secretion and contributing to lactation in mammals – a truncated list for sure.

What of the steroid hormones? Of the steroid-mediated processes that show widest variation in the vertebrates, reproduction ranks high in the list. The steroid hormones are thought (generally) to be essentially identical across the vertebrates, and the same groups of steroids, oestrogens and progestagens are present throughout. Indeed, it is this area that led Medawar to his near-aphorism.

It’s in the evolution of corticosteroids that things may seem muddy. Once upon a time, I thought that the first evolutionary appearance of

zonation in the mammalian adrenal cortex nicely coincided with the separate production of glucocorticoids and mineralocorticoids, because it’s only in mammals that they have distinct functions. It’s too neat: the mineralocorticoid-secreting glomerulosa, the glucocorticoid-secreting fasciculata (and the general glory hole of the reticularis making androgen, sulphoconjugating, and xenobiotic-metabolising) was never as clear as that.

Somehow or other it’s mostly the term ‘glucocorticoid’ that has misled us all. If we understood the essential functions of glucocorticoids, we might begin to understand why mammals appear to require a whole specialised cell type, with its own trophic factor, to make them. From the start it never was thought to be just about carbohydrate metabolism. But the range of functions in which glucocorticoids appear to have a role is huge, and finding a unified physiological and evolutionary explanation for a single control system is elusive.

Even if the actions of mineralocorticoids and glucocorticoids were neat, separated, discontinuous, how could that be explained by the promiscuity with which each binds to the other’s receptor (MR and GR) which, moreover, bind to the same response elements in the promoters of target genes?

Recent studies by Bridgham *et al.* (*Science* 2006 **312** 97) on the evolution of corticosteroid receptors show very nicely that MR and GR binding affinities for aldosterone and cortisol are discriminatory even in teleosts, in which aldosterone isn’t generally secreted at all. We should look at fish physiology to speculate how the uses to which the corticosteroids are put have evolved.

Marine teleosts, you might think, don’t actually need aldosterone. They have no trouble getting enough sodium, their problem is getting rid of it. So they excrete sodium across the gills (and kidneys), a process stimulated by, well, a ‘glucocorticoid’ – cortisol in fact. Those that live in fresh water have the opposite problem, vanishingly low availability of sodium, so they have a highly effective kidney that (with the gills) resorbs sodium aided, yes, by cortisol again. Associated with this, they must eliminate relatively vast volumes of water, perhaps also facilitated by cortisol.

***‘We should look at fish physiology to speculate how the uses to which the corticosteroids are put have evolved.’***

Here we come across a concept more familiar to a mammalian endocrinologist, for the elimination of a water load, and indeed shifting of water between body compartments, is an important ‘glucocorticoid’ function in mammals. But we are like neither marine nor fresh water teleosts. We terrestrial vertebrates are somewhere in between. Perhaps we’re more like euryhaline or estuarine fish, or fish whose watery habitats dry out occasionally. We too have the potential to be subjected to big changes in the availability of water, and of sodium.

So perhaps our ancestors didn’t crawl out of the sea at all. They came out of an estuary, or were left high and dry by capricious tides. But they were fully prepared, or ‘preadapted’, being equipped with limbs, lungs, a ‘glucocorticoid’ and a balanced set of MR and GR.

The rest is history.

GAVIN P VINSON

*You will find an obituary for Gavin Vinson on page 30 of this issue.*

# ENDOCRINE EVOLUTION

WRITTEN BY STEPHEN G HILLIER

FIRST PUBLISHED IN ISSUE 94 (2009)

The concept of hormones as chemical integrators, flashing through the bloodstream to co-ordinate bodily functions, is well over a century old. However, the molecules from which the first steroid hormones developed are estimated to be over 4,000 million years old, and the endocrine system in which they participate has been evolving ever since the first prokaryotic organism existed.

Our understanding of hormone evolution has leapt forward with the application of genome screening to phylogenetics and the emergence of molecular cladistics. Here, I briefly survey some elementary concepts of hormone evolution from the perspective of a steroid ‘anorak’.

As an unreconstructed steroid biochemist, I reserve the right to insist that steroid hormones rule, OK? Some pundits claim that steroids did not need to evolve – that they are in fact universal bioregulators that came with the big bang. It has been pointed out that steroids are omnipresent throughout the biosphere of the earth and the cyclopentanoperhydrophenanthrene nucleus is the ultimate primordial biomolecule. Some of the most primitive unicellular organisms have steroids and many bacteria biosynthesise and utilise these and related molecules. Even plants and invertebrates share the familiar acetyl-coA-mevalonate-cholesterol-pregnenolone pathway.

I particularly like the idea that endocrine steroid signalling may have co-evolved with cyclic AMP signalling. Steroids and cyclic AMP are thought to have co-existed in the planetary prokaryotic clone from which the first eukaryotes evolved.

Mycetozoa provide model systems for studying the origin and evolution of eukaryotes. The cellular slime mould (dictyostelid) has a vegetative growth phase during which individual cells exist as amoeba that feed on bacteria. When the food supply is exhausted, they aggregate to form a slug-like plasmodium, which develops into a spore-containing fruiting body. Once food becomes available, the spores are released to produce individual amoeba and the lifecycle starts anew.

The soluble communication factor that prompts amoeba to aggregate into the plasmodium is none other than ‘second messenger’ cyclic AMP. It has

been posited that cyclic AMP was a prototypic extracellular bioregulator that allowed elementary cell-to-cell communication but was unable to function as a true hormone owing to its chemical lability. On the other hand, the cell surface membranes of primordial unicellular organisms were probably composed of terpenoid derivatives such as steroids and retinoids that gained increasingly diverse signalling roles as metazoans emerged from the primordial gloom.

Present-day prokaryotes and eukaryotes share common biochemical mechanisms of steroid synthesis, action and catabolism. Thus the basic machinery necessary to evolve tissue-specific cell-to-cell signalling via steroids has been preserved across the plant and animal kingdoms. And throughout evolution, cyclic AMP has retained its quintessential communications function in the endocrine system.

The stereochemical determinants of steroid hormone specificity and potency prompt comparison with the impact of beak morphology on the adaptation of Darwin’s finches to their various food sources on the Galápagos Islands (see Figure).

We now know that paracrine cell-to-cell signalling involving bone morphogenetic protein-4 was responsible for the variation in beak size and shape among the finches he collected. Who knows, had Darwin been a steroid endocrinologist – in the right lab at the right time – correlation of steroid structure and function might have provided him with equivalent insights on natural selection to the Galápagos finches.

Hormone science has evolved beyond recognition since the term hormone was first coined in 1905. And 150 years after *On the origin of species*, pathway biology has emerged as the ‘fifth force’ in endocrinology, permitting mapping of the cellular receptors, downstream signalling molecules (including cyclic AMP) and attendant changes in gene expression through which hormones are produced and act on their cellular targets. Thus endocrinology has evolved into a diverse and dynamic specialty that integrates the molecules, mechanisms and medicines upon which post-genomic biomedicine is based. Surely, Darwin would have been impressed.

STEPHEN G HILLIER

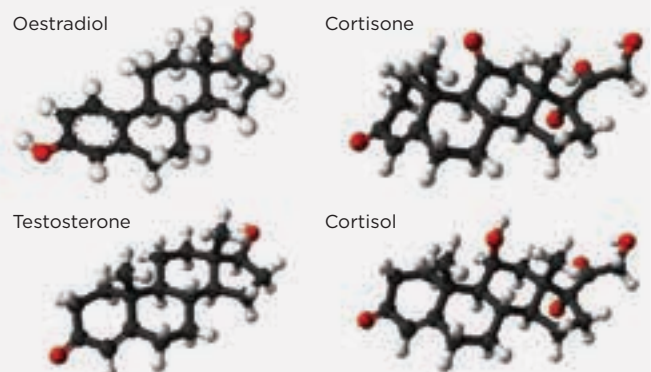
## FURTHER READING

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**Figure.** Darwin noted that finches on the Galápagos Islands had beaks of various sizes and shapes that were highly adapted to different food sources. Subtle differences in the stereochemical structures of steroid hormones such as those illustrated confer radical differences in target-tissue specificity and potency, consistent with an evolutionary pattern of steroid signalling in the endocrine system.



Finches from the Galápagos Archipelago



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# AGEING WITH CONGENITAL ADRENAL HYPERPLASIA

WRITTEN BY KAZ WILLIAMS



In this article, I touch on a range of experiences of living and ageing as a female adult with classical salt-wasting congenital adrenal hyperplasia (CAH). I was born in 1963 and have met and worked with many adults with CAH, both nationally and internationally. Ageing is a gradual process. We age in different ways: some we can influence, some not, but the earlier people with CAH engage in holistic dialogue about the ageing process, the greater our chances of improving our long term outcomes for well-being and quality of life.

## AVAILABILITY OF SUPPORT

Understandably, the medical and scientific community has focused on improving the treatment of CAH, and achieved widespread impact. Thanks to these efforts, the long term complications of CAH are better understood today. Moreover, partnership between the medical community and support groups has brought much positive change for the physical and mental health of people with CAH.

However, sadly, the attention given to the older cohort of people with CAH has been far from holistic, perhaps because CAH is a rare condition, for which treatment with glucocorticoids only started in the mid-1950s. Many women with CAH experience feelings of shame and stigma, and these feelings continue throughout the life course.

More change is needed. People with CAH want to meet others with the same condition. The transformative impact of coming together should not be underestimated. This needs to happen on a universal and sustained basis that is embedded in the wider care pathway. Thus, we share ways to take care of ourselves based on experience, and we help each other to believe we are worth taking care of, and that we do have some control in improving our own health outcomes, especially as we age. Peer support helps to heal those painful, concealed parts of ourselves that we have never shared; it helps us internalise the belief that we don't need to accept poor health and diminished lives.

## MANAGING CAH

Common concerns of adults with CAH are included in the panel below.

### SOME CONCERNS OF ADULTS WITH CAH

- Loneliness and isolation
- Fertility and reproduction
- Increased impact of stress as we age
- Osteoporosis
- Complications from early surgeries
- Struggles at work
- Menopause
- Difficulties with medication
- Feelings of shame
- Lack of access to endocrinologists with sufficient knowledge of CAH
- Poor body image

Added complications come with co-morbidities. I was diagnosed with rheumatoid arthritis (RA) at the age of 50, and this added a new dimension to managing my own health and well-being. Having already lived with disability, I did not experience the trauma of a new diagnosis, and it has been a relief to have a condition that it feels OK to be open about, in spite of common misunderstandings about the impact of living with RA.

It has and always will be difficult to tell people I have CAH. I have had to find my own way to manage this co-morbidity, not least because, while many adults with CAH also have an inflammatory condition, getting an understanding from the medical profession on how the conditions interact has been challenging. In my experience, aspects of the two conditions can mimic each other; flare-ups of RA impact the adrenals and vice versa.

## CARE OF YOUNG PEOPLE: PAST AND PRESENT

I have been fortunate in the care I have received. I could be critical of the abuse received at the hands of medics as a child and adolescent, some of which were specific to having CAH. However, much of this was mirrored in the treatment of many disabled children in the 1960s and 1970s. Most painful and unacceptable is the fact that much of this abusive practice continues today, though now there is no 'excuse', as clinical guidelines exist – as does extensive literature on trauma, early surgery and the long term impact of adverse childhood experiences.

*'We need a new dialogue in which we are not seen as having a disease, being disordered or in need of fixing.'*

## WORKING TOWARDS A BETTER FUTURE

There is no doubt endocrinologists are passionate about improving their patients' quality of life. I owe a debt of gratitude, as do so many others with CAH, to the multidisciplinary teams that have saved our lives, advanced the research and tirelessly worked to improve care and treatment.

However, to bring about further improvements in our health and well-being, a stronger partnership is needed with those with CAH and groups supporting people with a range of variations of sex characteristics. Healthier, happier, more fulfilled and well informed adults with CAH help relieve an already overloaded NHS. With the right support, we can manage much of our own care ourselves. Drawing on clinical, peer and personal resources helps us find what works for us, both collectively and individually, especially as we age.

We need a new dialogue in which we are not seen as having a disease, being disordered or in need of fixing, a dialogue that recognises the pride in the difference that girls and women with CAH have, so that we can embrace all parts of ourselves without shame and secrecy, and thus start the process of healing and ultimately true self-care and love.

## KAZ WILLIAMS

Adult Support Co-ordinator [kaz@cah.org.uk](mailto:kaz@cah.org.uk)  
CAH Support Group [www.livingwithcah.com](http://www.livingwithcah.com)

# We speak to your new GENERAL SECRETARY AND PROGRAMME SECRETARY

## RUTH ANDREW, GENERAL SECRETARY

Ruth Andrew is a research scientist in the Centre for Cardiovascular Sciences at the University of Edinburgh, where she studies steroid hormone action in metabolic disease, and how innovations in mass spectrometry can be applied to give greater insight into steroid biochemistry and, more broadly, lipid biology.

### WHAT INSPIRED YOU TO TAKE UP RESEARCH?

I enjoy making things work, so I've chosen to tackle research from a perspective that bridges chemistry and biology. To that end, I elected to study analytical chemistry as my specialist subject in my summer studentship and honours project during my undergraduate pharmacy degree. Anyone who works with mass spectrometry instruments knows you need to be good at making things work and troubleshooting!

My undergraduate supervisor studied catecholamines, which led me to continue in endocrinology, with the massive switch from the adrenal medulla to cortex when I took up my first postdoctoral position in Edinburgh. Endocrinology offers you the chance to learn about integration of body systems, and steroid biochemistry presents lots of challenges that we can't answer because we don't have the right technology (or we do, but haven't applied it).

I like researching ways to overcome hurdles in understanding steroid biochemistry from a chemistry perspective. And I admit I like playing with fascinating new approaches to mass spectrometry and new instruments. I've never lost the joy and satisfaction of a Friday afternoon managing to separate two steroids that were resolutely previously indistinguishable, seeing them come apart in your hands by chromatography – or now ion mobility – is really satisfying.

### WHAT ARE YOU PROUDEST OF IN YOUR CAREER, SO FAR?

I'm proud of our translational studies on the metabolic role of glucocorticoids and 5 $\alpha$ -reductase inhibitors, which have come from cell and animal studies through to population-based pharmacoepidemiology. It feels a huge achievement to have made a difference to patients.

I'm also very proud of what our mass spectrometry group has contributed to endocrinology, with mass spectrometry imaging. It's good to see the current increased recognition of the role of specialist technologies/ists in academia. I'm also really proud when I look at the achievements of the students and postdocs I've worked with, and how they are now independently contributing to many areas of endocrinology and beyond. I'm very glad that I have the chance to continue working with many of them as they advance through their careers. I'm grateful they still want me around!

### WHAT ARE THE MAIN CHALLENGES FOR ENDOCRINOLOGY AND THE SOCIETY?

At the moment, I think the main challenge is to try and heal the career wounds inflicted by COVID on the Society's early career members. Many have had their studies interrupted, have had to study remotely, have had research projects delayed, or have had harrowing clinical duties, and the impact may not fully show for a few years.

They are being affected silently through losses in network building and face-to-face interactions, e.g. at conferences. These situations build

confidence and breadth of knowledge. There are also more overt impacts on productivity or portfolio of work. I think, as a Society, we have the challenge of finding the best way to support that cohort of future endocrinologists as we try to get back on track, but we can play a role here that is harder for bigger institutions (such as UK Research and Innovation), through our more personal approach and closer network.

### WHAT DO YOU HOPE TO ACHIEVE DURING YOUR TERM?

I'd like to increase the visibility of types of careers in endocrinology that are available, beyond what might be classically considered, for example, by encouraging more engagement with educators, vets and industrial scientists.

### WHY DID YOU GET INVOLVED WITH SOCIETY GOVERNANCE, AND WHY SHOULD OTHERS?

I was encouraged to join the Society at an early stage by Brian Walker and I found the SfE BES conferences very enjoyable and inclusive. I joined the Science Committee in a bid to broaden my expertise and network. I still remember coming away from my first meeting, chaired by Alan McNeilly, where we'd discussed Early Career Grants and other ways to support students, and feeling I had made a positive contribution. I came home saying "I've done good today!"

That led me to volunteer for more roles. One important one was in co-organising the Career Development Workshops from the beginning. The feedback we had from the attendees was so overwhelmingly positive, and I got a real sense of satisfaction in helping them. More than that, I made many friends, especially Derek Renshaw, who was at a similar stage in his career to me. It's good to hear academic perspectives beyond Edinburgh.

From there, I've been involved with other committees and in every one, I've broadened my perspective and brought what I've learned to other aspects of my job. I find the Society has a very 'we can do this' attitude, and we are given huge support from the Society's team to make an impact. It's a pleasure to work with people who want to make endocrinology in the UK better, and who have your back as you try to achieve that. I'm hugely grateful to Eleanor Davies who has guided me in my approach to being General Secretary, and I know I can always call on her for help.

### ANY WORDS OF WISDOM FOR ASPIRING ENDOCRINOLOGISTS?

Career-wise – work out what you enjoy and who you like working with and be persistent. Life's too short to be stuck doing something you dislike. Get used to picking yourself up and trying again. Try to be objective and not emotional about your career decisions – it can take a few days after that grant rejection or paper rebuttal to achieve that, but you need to conquer that skill.

Working on Society activities will repay you in many more ways than you can possibly imagine, so get involved. Citizenship roles in the Society feel really rewarding and will help you past bumps in your career where maybe your day-to-day work is not quite what you desire!





## ROBERT SEMPLE, PROGRAMME SECRETARY

Robert Semple is Chair of Translational Molecular Medicine at the University of Edinburgh. He also does outpatient clinical work in diabetes and endocrinology for NHS Lothian. In addition to overseeing biomedical PhD training, he spends most of his time running a research programme. His research focuses on how insulin signalling and fat tissue work in health, and how this goes wrong in disease. His research starts with, and focuses on, people with rare and severe types of disease, often caused by changes in a single gene. To investigate these fully, his lab also studies cells and model organisms.

### WHAT INSPIRED YOU TO TAKE UP RESEARCH?

I can't imagine not wanting to solve puzzles, and I have always found the diagnostic process hugely rewarding. I see my research as an extension of this. Instead of being constrained by established wisdom (sometimes wrong) and available clinical tests, I like to take tricky diagnostic problems into the research lab and try to think, with my team, of ways to uncover the truth. I am always alert to lazy diagnostic thinking that doesn't stand up to rigorous scrutiny.

As for endocrinology, I was studying biochemistry and molecular biology just when the way insulin works on cells was being discovered. This fascinated me scientifically and, when I learned more in subsequent clinical training about the poorly understood, but enormous, medical problem of type 2 diabetes, I was hooked. Mind you, I still remember the snort of derision from a consultant general surgeon when I told him, in the operating theatre as a student, that I already wanted to be an endocrinologist!

### WHAT ARE YOU PROUDEST OF IN YOUR CAREER, SO FAR?

Goodness, that's a question I'd rather defer to my retirement! Honestly, it is the contribution to the all-round enterprise – clinical care, teaching, and research – that I am most proud of. But every time we have discovered a new cause of a disease (usually genetic) it has been particularly exciting and satisfying, especially where this has given insights into human biology and suggested routes to treatment.

Recent examples have been identification of changes in insulin signalling genes that leave them 'stuck on', causing severely low blood glucose or excess tissue growth. Unlike many genetic discoveries, these findings suggested immediate new options for treatment, in this case with drugs which were initially developed for cancer. These are currently working through clinical trials.

### WHAT ARE THE MAIN CHALLENGES FOR ENDOCRINOLOGY AND THE SOCIETY?

These must be recruitment and retention of the brightest and best clinicians and scientists.

Endocrinology is a wonderful and diverse specialty full of big unanswered questions and terrific science, but it now competes with

other disciplines, where exciting advances are also being made.

The best of the specialty can sometimes be hidden from clinical trainees by the demands of routine, ward-based care. So, we all need to get out and make the case to students and junior doctors for our specialty, and also make it easy for the brightest scientists, who are mobile among disease areas, to identify themselves as endocrine researchers.

### WHAT DO YOU HOPE TO ACHIEVE DURING YOUR TERM?

I inherit a really good team and a robust system for assembly of the SIE BES programme from Duncan, which includes strong input from the Endocrine Networks. So, no revolution is required. However, it is crucial to pick up strongly after the long COVID-19 hiatus with the most exciting programme possible, and to constantly look out for any emerging areas of interest where we can introduce fresh content and formats. If SIE BES is still a highlight of the year for clinical colleagues, endocrine scientists and all types of trainees in three years, then my job will have been done!



*'We all need to make the case to students and junior doctors for our specialty, and make it easy for the brightest scientists to identify themselves as endocrine researchers.'*

### WHY DID YOU GET INVOLVED WITH SOCIETY GOVERNANCE, AND WHY SHOULD OTHERS?

It was enjoyment and duty, wrapped up together. Putting together the SIE BES conference means working with interesting colleagues and horizon-scanning the best endocrine science and clinical practice, and is intrinsically rewarding.

There is pressure too, of course, to continue to find the balance that satisfies all types of member, but I fundamentally believe that, having taken so much from SIE BES over the years, it is right to try to contribute something back, so that others can have the same experiences. Anyone who has enjoyed SIE BES, especially if they have spotted things they think could be improved, should try to get involved. It's our meeting and it is what we make it!

### ANY WORDS OF WISDOM FOR ASPIRING ENDOCRINOLOGISTS?

Treat people, not diseases, and value the insights of colleagues. But when you see something that you don't understand, or that doesn't seem to fit with conventional wisdom or the algorithm of the moment, don't be *too* respectful. Ask the difficult questions and point out that 'the emperor is wearing no clothes', when necessary!

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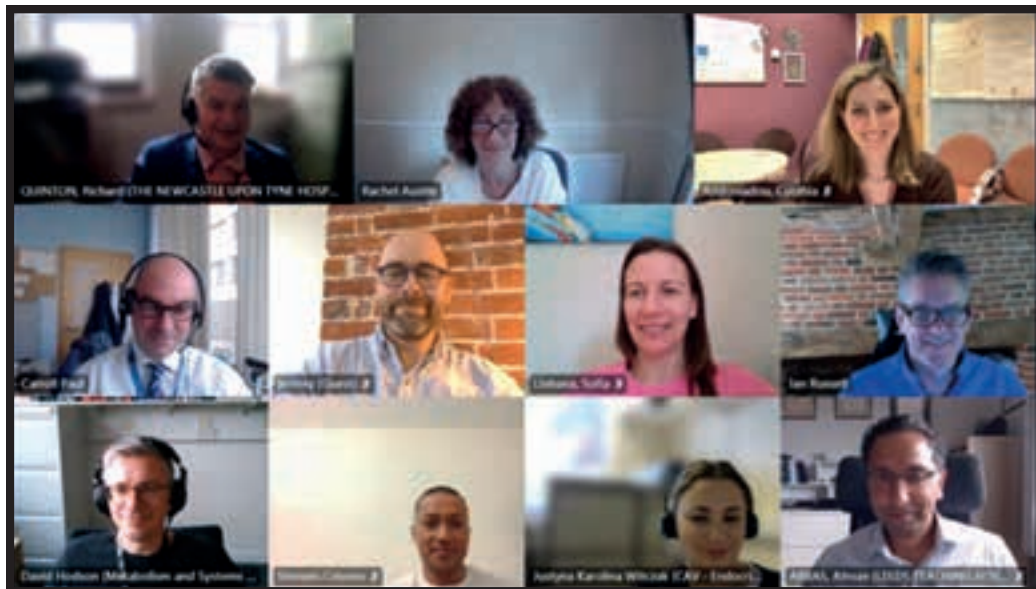
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# Collaboration with industry: **SHAPING ENDOCRINE CARE**

WRITTEN BY PAUL CARROLL AND JEREMY TURNER

The field of endocrinology and the Society for Endocrinology have a long history of collaboration with commercial partners and the pharmaceutical industry. Sponsorship and support from industry are essential for the successful delivery of Society activities and events, facilitating the work done by the Society on behalf of its members.



Virtual Corporate Liaison Committee meeting, autumn 2021.

Endocrinology has a rich history of effective working with the pharmaceutical industry on drug discovery, conduct of clinical trials and making new treatments available in a responsible and cost-effective manner. As members will know, the regulation and nature of the pharmaceutical industry have changed over the last decade. The Society recognises the need for a continuing, but also refreshed, relationship with pharma and non-traditional industry partners (e.g. the med tech and devices sector). This relationship must be mutually beneficial, appropriate, in keeping with the ethos and code of practice of the Society and represent the views and wishes of our members.

## **CORPORATE LIAISON: FOSTERING RELATIONSHIPS**

The former Corporate Liaison Board was 'upgraded' to the more comprehensive and empowered Corporate Liaison Committee (CLC) in 2018. The CLC includes broad representation of Society members from clinical and scientific backgrounds and has excellent Society support. It operates in close collaboration with the other Society committees, Council and senior staff. Meeting regularly, the principal remit of the CLC is to foster and oversee the relationship of the Society with industry partners. Rachel Austin and Sophie Tovey from the Society Engagement Team provide excellent support and direct liaison with our industry colleagues.

*'Working closely with industry remains at the heart of discovery, innovation, and development of new diagnostics and treatments for endocrine conditions.'*

The CLC has modernised its *Policies for Working with Industry*, to ensure appropriateness of interaction and liaison. It has supported a change in emphasis for interaction with industry, moving from a purely 'transactional' relationship to one where we create more bespoke models of working with key partners. This tailored model is in place for our work with a number of companies, with excellent examples of Society members contributing to product design, clinical trials, licensing applications, industry staff training and access to key opinions. There is also the opportunity for industry partners to support Society staff, sharing corporate knowledge and resourcing.

## **WELCOMING INDUSTRY PARTNERS AT SfE BES**

In addition to traditional large companies with established portfolios in the endocrine area, we are seeing the emergence of smaller and newer companies, often tailored to rare diseases in endocrinology. Newer, non-therapy-based companies, involved in diagnostics, imaging, laboratory materials and 'med tech' are emerging. This year, seven new industry partners attended and exhibited at SfE BES 2021. The CLC has encouraged medical and scientific staff from industry to join the Society and attend and contribute to the SfE BES conference. We invite you to please make all our colleagues from industry feel welcome and valued at SfE BES conferences and other Society meetings.

## **WORKING AT THE HEART OF INNOVATION**

Working closely with industry remains at the heart of discovery, innovation, and development of new diagnostics and treatments for endocrine conditions. Establishment of the CLC ensures that the Society has a clear mechanism for overseeing and developing our relationship with industry partners. The CLC and the entire Society are very grateful to all who continue to contribute to this forward-looking and modern approach to industry collaboration, at a time when agility and commitment are needed.

The CLC is always looking for new members to join and contribute to the Committee. We need broad representation, reflecting the membership of the Society. Please consider applying; it is a real opportunity to contribute and shape endocrine care for the future.

Finally, we are also delighted to announce that Jeremy Turner has accepted the post of Chair of the CLC, commencing January 2022. We welcome Jeremy to this new role, recognising that he will have success, make friends and have fun along the way!

**PAUL CARROLL AND JEREMY TURNER**  
Retiring and Incoming Chairs, Clinical Liaison Committee

Visit [www.endocrinology.org/corporate-liaison-committee](http://www.endocrinology.org/corporate-liaison-committee) to find out more.

# CREATING A BETTER FUTURE FOR ENDOCRINOLOGY: A JOINT EFFORT

WRITTEN BY MARTIN REINCKE

## THE WORLD NEEDS MORE ENDOCRINOLOGY!

Throughout the world, the number of patients with endocrine diseases is increasing, posing a vast challenge and a stress on healthcare structures, demanding increased allocation of healthcare resources and, ultimately, having a long term impact on the fabric of society itself. The chronic nature of endocrine diseases adds to the general burden on society.

The projections around the percentages of the population suffering from obesity, diabetes and the associated cardiovascular diseases and mortality are dramatic. Endocrine-related cancers are on the rise. Rates of fertility disorders and problems are increasing. The societal burden of rare diseases (including endocrine-related ones) is high on the agenda and continues to require new pathways to innovation and research resources. The challenge posed by environmental factors such as endocrine-disrupting chemicals may be accepted by some policymakers, but there's a long way to go towards reducing exposure to these chemicals. And, very recently, the emergence of the pandemic has unveiled the huge impact of obesity and diabetes on mortality in individuals infected by the COVID-19 virus.

## ENDOCRINOLOGY - WHAT?

This question is still a too frequent initial reaction when, as endocrine professionals, we want to draw attention to what our discipline means for the health of citizens around the world.

We need to recognise that, as a medical discipline, we are primarily present in secondary and tertiary healthcare structures. I would suggest that, too often, endocrinology remains distant and invisible from the mainstream discussions around healthcare – though some of the diseases we represent are very much part of the most pressing challenges our healthcare systems face right now.

Additionally, the number of healthcare providers engaged in our discipline is relatively small compared with the 'bigger disciplines' like cardiology or oncology (just to name two that most readily come to mind). A recent survey conducted by the European Society of Endocrinology (ESE) with national endocrine societies from 50 countries across Europe counted around 22,500 endocrine professionals. When recalculated, this equates to an average of 19 endocrinologists per million inhabitants (range 9–100 per million!). This survey also highlighted a number of the key issues we face, such as a general lack of understanding of endocrine health, under-funding of research, and a need to attract more people to endocrinology, amongst others.

## A NEED FOR A EUROPEAN COLLABORATIVE EFFORT?

Yes, I am aware that there can be different perspectives around health and research policies and the national structures of healthcare, but I do believe that the things that unite us are stronger than the areas where we differ. And that definitely goes for a medical discipline like endocrinology.

I would postulate that every European country has the benefit of:

- access to research collaboration across borders and increased resources
- access to well-trained staff, with standards of education becoming more uniform across the continent
- staff who can move easily around Europe, so that opportunities for the individual and for the healthcare structures open up
- opportunities for patients to have access to across-the-border clinical care, primarily for those suffering from rare or ultra-rare diseases.

The suggestion that some countries would be reluctant to fully engage because they would expend more effort than the rewards they would reap is not new, and needs to be challenged. There's something here for everyone.

Just two areas where I can see a benefit for many countries are:

- the engagement in research without borders (including tapping into European funding mechanisms)
- hospitals' need for skilled healthcare professionals with a good education, that may rely on mobility across Europe.

And for those countries where (due to size or economic considerations) healthcare structures, education and access to top-notch technologies and care are still problematic, the collaboration can and must offer a different perspective.

The solution can only be achieved within the framework of a collaborative European effort, much of which relies on a voluntary, engaged approach by all stakeholders. It is our aim that this should ultimately impact upon healthcare and research policies recognising the importance of endocrine health and disease.

## ENTER ECAS

The collaborative effort in all its different dimensions and across national borders is one of the reasons for the existence of ESE. **Our vision is**



# European Society of Endocrinology

to shape the future of endocrinology and we do so by uniting, representing and supporting the discipline.

Structures with the label 'European' can be perceived as challenging or competitive to national structures. The generally accepted principle of subsidiarity – the higher (European) level should only take action collectively when action at the lower (national) level is not effective (enough) – should also apply to the relationships between national and European medical societies, including ESE.

The **ESE Council of Affiliated Societies (ECAS)**, a council with representation from 54 national endocrine societies from 44 countries in Europe, is at the heart of this principle and collaborative effort. Initiated in 2013, it has had an instrumental role in taking initiatives that address some of the challenges described above.

## THE WHOLE IS GREATER THAN THE SUM OF ITS PARTS

The introduction in 2016 (with revision in 2019) of the **European Curriculum on Diabetes, Endocrinology and Metabolism** has set a common standard across Europe with regard to the expected knowledge and skills for endocrinology. It is reflected in the ESE European Postgraduate Course programme and the European Board Examination (organised for the first time in 2018, together with the Royal College of Physicians and the European Union of Medical Specialists). More than 200 endocrinologists have now taken this exam.

*'There can be different perspectives around health and research policies and the national structures of healthcare, but I do believe that the things that unite us are stronger than the areas where we differ.'*

The development of the **ESE Centres of Special Interest** programme paves the path towards greater collaboration between European academic institutions in terms of joint research interests, staff exchange and educational exchange programmes. More is yet to come, with the valuable addition of initiatives from the **ESE Young Endocrinologists and Scientists**, in the form of their Clinical Observership Programme and the new Research Observership Programme.

The launch of the **ESE White Paper** in 2021, entitled *Hormones in European Health Policies*, addresses the priority areas for European endocrinology. It is here, as well, that ECAS and ESE's National Affiliated Societies have played a major role in informing, prioritising and committing to the areas where endocrinology needs stronger policy engagement. In order to generate the ultimate benefit to patients around Europe, the efforts at the European level cannot be disconnected from a joined up effort at national level (most healthcare policies being the responsibility of national governments). ECAS will continue to have an important role to play here in the years ahead.

Members of the National Affiliated Societies represented in ECAS (which include the Society for Endocrinology) can sign up to **ESE membership** at reduced rates and enjoy a wide range of benefits, including substantial reductions in fees for registration for ESE events or for access to journals, as well as grant support. Through signing up to the **ESE Advocacy Representative Scheme**, societies and individual members can now

build a stronger voice to be heard by policymakers, both at European and national levels.

## A STRONGER VOICE FOR ENDOCRINOLOGY - A SHARED RESPONSIBILITY

ESE, together with its partner societies with a national or specialist endocrinology interest, is fully committed to creating a better future for endocrinology. The collective aim must be to ensure that endocrinology remains an attractive and stimulating workplace for healthcare professionals, and an area for ongoing research and clinical investment. The goal is to secure better conditions around endocrine health and care for the increasing number of patients across Europe.

This, dear colleagues, is solely up to us, as endocrine societies, through the collaborations we foster, and also through the interest and engagement of every individual endocrine professional.

**MARTIN REINCKE**  
President of the European Society of Endocrinology

# GAVIN VINSON: A CURIOUS ENDOCRINOLOGIST 1939–2021



Few who knew him would not agree that Gavin Vinson was one of the truly colourful characters in British endocrinology over the last half century. Many will recall his contributions to Society meetings, not only in the lecture theatre, but also in providing the musical entertainment at our receptions, and on the dance floor after conference dinners.

Sadly, Gavin died earlier this year, after a long illness. We felt it important for members of the Society to remember this extraordinary man who strongly supported and contributed to this organisation.

Although born in Cornwall shortly before the Second World War, Gavin grew up in London during the Blitz. He excelled at school and, although considered for Oxbridge, he chose to read zoology at Sheffield University. He threw himself into university life (as he did into most things) and always retained very fond memories of his time as an undergraduate. Here, through his musical involvement in the orchestra, he met Bronwen, his future wife.

After graduation, he remained at Sheffield to undertake a PhD under the supervision of Ian Chester-Jones, on the comparative biology of the adrenal cortex and its function. This was a highly productive period with a dozen papers coming from his PhD alone (mostly published in *Journal of Endocrinology*). It set the focus for his lifetime research interest.

His enormous productivity continued as a junior lecturer in Sheffield with his student Barbara Whitehouse, before he and Bronwen grasped the opportunity to move to work with John Phillips in Hong Kong for a year.

It was from here that, in 1967, he was recruited by Dennis Lacey to take a junior lectureship in zoology at Barts in London, so beginning a long-lasting relationship with this institution in its various manifestations.

Gavin maintained his research productivity and rose through the academic ranks, joining the Department of Biochemistry in 1980, where he became Professor of Biochemistry and Head of Department in 1985. The storm clouds were gathering over the rather tranquil ivory towers of Charterhouse Square by this time. In 1989, the preclinical schools of Barts and The London Medical Colleges were merged and moved to the Queen Mary and Westfield College campus in Mile End. This was a precursor to the complete merger of the two medical schools and their merger with Queen Mary in 1995. Gavin remained as Head of Biochemistry and became Dean of the Faculty of Basic Medical Sciences in 1994. One would be correct in thinking that this was a very difficult and highly charged time, as the individualities of three very distinct institutions were blended into one. The fact that, today, these conflicts are history is in some part due to Gavin's leadership.

Despite these difficult times, the research productivity of the Vinson lab persisted, with the support of Joy Hinson, Pete Raven, Stuart Barker, Robert Abayasekara, John Puddefoot and many others. The focus remained on adrenal steroidogenesis, and the group was at the forefront in describing the importance of adrenocortical blood flow in the regulation of this process, as well as aspects of the roles of adrenocorticotrophin, angiotensin and other peptides in adrenal function.

Gavin had always been closely involved in the Society for Endocrinology. In 1983, he received the Society for Endocrinology Medal. In 1985, he became Editor-in-Chief of *Journal of Endocrinology* – a role that he held for seven years. When he became Editor, this was the Society's only journal, and its worldwide subscriptions provided the Society's main source of income.

*'Gavin was a highly talented man whose science was driven by curiosity, a talented musician and a keen linguist, who supported our Society and, in particular, the careers of young endocrinologists.'*

Gavin had always been interested in music and had become a highly accomplished jazz and classical pianist. Not infrequently, one might be enjoying a beer or a meal with Gavin in an establishment with live jazz, and he would quietly go up to the pianist, exchange a few words with them and replace them on the stool. What followed was usually a fantastic jamming session that had everyone highly entertained. In retirement, Gavin took up making stringed instruments from their basic components. He completed a formal training in this skill and completed a viola (as shown in the photograph) and, most recently, a cello – a present for his daughter.

Gavin was a highly talented man whose science was driven by curiosity, a talented musician and a keen linguist, who supported our Society and, in particular, the careers of young endocrinologists. He leaves his wife, Bronwen, his two daughters, one son and five grandchildren, and will be missed by many former students, technicians, researchers and colleagues.

ADRIAN CLARK AND IAN MASON

# ROGER VALENTINE SHORT: LOOKING AT THE BIG PICTURE

## 1930–2021

Roger Short was born Weybridge, Surrey. It was in his childhood that he started to develop his love of animals, his passion for learning and his powerful story-telling.

Talking about this period in an interview for ABC Radio's 'The Science Show', he recalled "I spent every day of my life on my boat, with my little dog Sam sitting in the bow, drifting down the river. It was an absolutely fantastic childhood. That gave me a love of wildlife and I got very interested in fish. I found that I was rather good because I could get up at dawn and go spinning in the Thames and catch these great big pike which no one else could catch. I thought, 'I don't want to kill them, I want to put them back. But I want to show somebody that I've caught them.' So I gill-tagged them and, at the age of 16, I wrote my first paper, a letter to *The Field* magazine on the growth and movement of pike in the Thames, by capture and recapture of my tagged pike."

He subsequently authored over 400 scientific publications!

Roger's academic education began at the University of Bristol where he studied veterinary medicine. He was awarded a Fulbright Fellowship to the University of Wisconsin, where he graduated with a Masters in genetics. His PhD followed in 1958, supervised by Thaddeus Mann at the University of Cambridge. Here he met his first wife, Mary. They became parents to Nick, Fiona, Clare and Kim. Roger continued his work in Cambridge as a lecturer then reader, and as a member of the Unit of Reproductive Physiology and Biochemistry. He was awarded a Doctor of Science in 1969.

Roger's research spanned 60 years and an incredible breadth of topics, from elephants to AIDS, from marsupials to mules and from condoms to camels, including the first camel–llama hybrid, Rama the Cama. Roger was the first person to isolate and measure progesterone; he published this research in his first paper in *Nature* in 1956. He also initiated work on embryonic

diapause in badgers and roe deer, and supervised projects on horse and elephant reproduction.

His mind was ever-curious and always thinking of the next big idea, tackling the 'big picture' questions and letting those who followed fill in the detail. Whilst working in Cambridge, Roger realised that controlling human population growth was critical to wildlife conservation – triggering the next phase of his career on human reproduction. He coined a phrase on conservation action: "if you are only talking it, it's conversation".

*'A gifted teacher, Roger covered the topics of contraception, world population growth, breastfeeding, abortion, human population, reproductive biology, fertility and especially HIV/AIDS.'*

Roger was the recipient of many honours and awards, including the Society for Endocrinology Medal in 1970. In 1972, he moved to Edinburgh to establish the MRC Unit of Reproductive Biology, which he directed for ten years. During this period, he was also an Honorary Professor at Edinburgh University. He was elected a Fellow of the Royal Society in 1974. In 1982, Roger moved to Australia to take up a Personal Chair in Reproductive Biology at Monash University in Melbourne. He married his second wife Marilyn in Canberra, and they had two daughters, Tam and Kirsty.

A gifted teacher, Roger covered the topics of contraception, world population growth, breastfeeding, abortion, human population, reproductive biology, fertility and especially HIV/AIDS. Students the world over still fondly remember his lectures.

In Melbourne, Roger's creativity and innovative thinking continued. He patented melatonin's use to treat jet lag; he worked on HIV/AIDS and was a member of the World Health Organization AIDS Taskforce; with his wife Marilyn, he studied the contraceptive effects of breastfeeding. He was a tireless campaigner for limiting world population growth (despite somewhat ironically having six children of his own).

In the 1970s, Roger co-authored a series of textbooks with Bunny Austin entitled *Reproduction in Mammals*, which remain classics in the field. However, his favourite book was *Ever Since Adam and Eve*, co-authored with Malcolm Potts. It sold over a million copies and was translated into Spanish, Italian, Korean and Chinese.

Instead of retiring when he left Monash University in 1995, he became Wexler Professorial Fellow at the University of Melbourne, continuing to share his passion for teaching and learning. He initiated a 'Teach the Teacher' programme for final year medical students to lecture final year education students on puberty, contraception and abortion.

Roger Short AM FRSE FRS FAA was a great scholar, researcher, teacher, mentor and raconteur. He will be missed, not only by his family and for his extensive research output, but also for his friendship and the twinkle in his eye. He is survived by his second wife, Professor Marilyn Renfree AO FRS FAA, and family in the UK and Australia.

JOCK FINDLAY, GEOFF SHAW AND PETER TEMPLE-SMITH



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